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A Randomized Controlled Evaluation of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence (BRAC)

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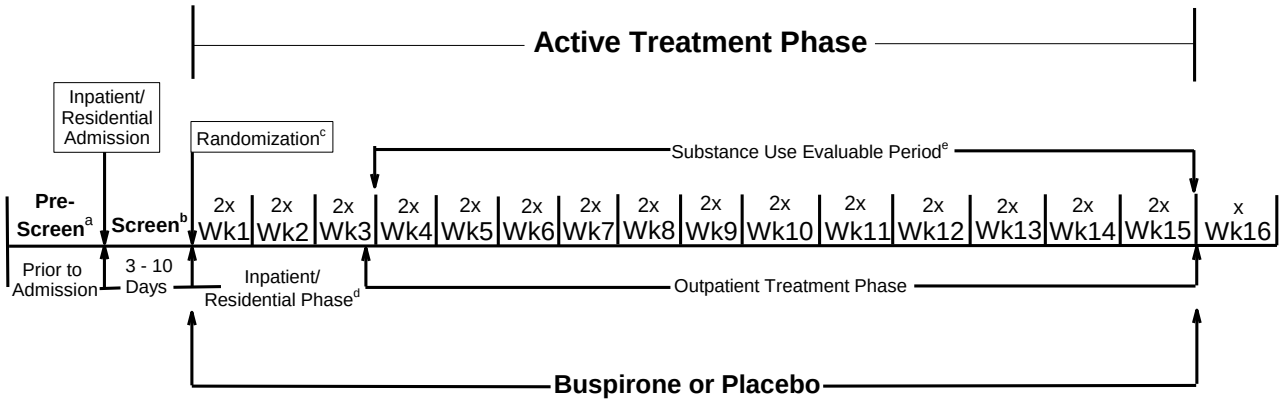
1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CRF	Case report form
CDMC	Centralized Data Management Center
CCC	Clinical Coordinating Center
CCQ-Brief	Cocaine Craving Questionnaire-Brief
CTN	Clinical Trials Network
CTP	Community treatment program
CAS	Composite Adherence Score
CM	Contingency management
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision
DA	Dopamine
FrSBe	Frontal Systems Behavior Scale
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IRB	Institutional Review Board
ITT	Intent-to-Treat
LI	Lead Investigator
LN	Lead Node
MC	Medical Clinician
MEMS	Medication Events Monitoring System
MSO	Medical safety officer
NIDA	National Institute on Drug Abuse
OCDUS	Obsessive Compulsive Drug Use Scale
1-PP	1-(2-pyrimidinyl) piperazine
QA	Quality Assurance
RAB	Risk Assessment Battery
RA	Research assistant
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TLFB	Time-line follow-back
TAU	Treatment as Usual
UDS	Urine drug screen
WHOQOL-BREF	The World Health Organization Quality of Life (WHOQOL)-BREF

2.0 STUDY SCHEMA

Figure 1: Study Schema



Notes:

[a] Pre-screen prior to admission is optional.

[b] Screening/baseline starts post-inpatient/residential admission and lasts a minimum of 3 days and a max of 10 days; retrospective screening/baseline measures will assess the period before inpatient/residential admission.

[c] Randomization can occur on days 3-10 of inpatient/residential stay when participant has~12-19 days remaining in scheduled inpatient/residential stay.

[d] The scheduled inpatient/residential treatment phase is approximately 12-19 days long.

[e] For substance use outcomes, the evaluable period is study weeks 4-15.

x = scheduled research visit.

3.0 STUDY SYNOPSIS

STUDY OBJECTIVES. The primary objective is to evaluate the efficacy of buspirone, relative to placebo, in preventing relapse in cocaine-dependent adults in inpatient/residential treatment who are planning to enter outpatient treatment upon inpatient/residential discharge. Secondary objectives include evaluating the impact of buspirone, relative to placebo, on other drug-abuse outcomes and on factors that may mediate buspirone's efficacy as a relapse-prevention treatment.

STUDY DESIGN. A two-stage process will be used to evaluate buspirone in which a pilot study will first be completed to obtain information needed to design the full-scale clinical trial (e.g., information about medication tolerability, adherence, missing data rates, etc.). The pilot and full-scale trials will utilize similar treatment phases and outcomes with adjustments made as needed (e.g., to medication dosing, sample size estimates, etc.) to the full-scale trial based on the pilot data. Both trials will be a 16-week, intent-to-treat, double-blind, placebo-controlled, randomized trial. Eligible participants will be randomized to buspirone or matching placebo and will be scheduled to attend two research visits per week throughout the active treatment phase which begins with randomization and ends on day 7 of study week 15. A single visit will be scheduled in week 16 to complete retrospective data for week 15. Participants will be screened after being admitted to inpatient/residential treatment and will be randomized when they have approximately 12-19 days remaining of their scheduled inpatient/residential stay, allowing the 10-day dose escalation period to be completed in the inpatient/residential setting. Participants will receive buspirone or placebo throughout the 15-week active treatment phase. Randomization strata include study site and cocaine use frequency (<10 days or ≥ 10 days in the 28 days prior to inpatient/residential admission).

STUDY POPULATION. For the pilot trial, approximately 60 participants recruited from approximately six community treatment programs (CTPs), will be randomized. The number of participants for the full-scale trial will be determined based on data from the pilot trial but is estimated to be approximately 264 randomized participants. CTPs with an inpatient/residential treatment program, a local outpatient program that provides treatment post-discharge, and that are likely to meet the target randomization rates for the trial are eligible to participate with the goal of having the same six CTPs participate in both the pilot and full-scale trials. The study population will include adults who meet DSM-IV-TR criteria for cocaine dependence, are being admitted to an inpatient/residential treatment program with an expected 14-28 day stay, and plan to attend outpatient treatment post-discharge through at least the end of the active treatment phase.

TREATMENTS. Study participants will be randomly assigned to receive either buspirone or matching placebo. All participants will receive contingency management in which incentives are given for bottle-opening adherence as determined by the Medication Events Monitoring System (MEMS). All participants will receive psychosocial treatment as usually provided by the inpatient/residential and outpatient programs in which they are enrolled.

ASSESSMENTS. Drug-abuse outcomes include cocaine use as assessed by urine drug screens (UDS) and self-report of cocaine use, other substance use as assessed by UDS and self-report of substance use (i.e., alcohol and/or illicit drugs), cocaine binging, HIV risk behavior, quality of life, functioning, and substance-abuse treatment attendance. The primary outcome measure is maximum days of continuous cocaine abstinence, as assessed by twice-weekly UDS and self-report, during study weeks 4-15. Process variables include drug attentional bias, cocaine craving, and compulsivity. Safety measures include vitals, adverse events (AEs), and mood measures.

PRIMARY ANALYSIS. In both trials, the primary analysis will evaluate buspirone's efficacy, relative to placebo, in blocking reinstatement of cocaine use as assessed by the maximum days of continuous cocaine abstinence, as assessed by twice-weekly UDS and self-report, during study weeks 4-15.

4.0 BACKGROUND AND RATIONALE

4.1 Background

Cocaine addiction represents a significant problem as evidenced by the sheer number of lives affected, its associated medical and legal consequences, and the difficulty finding effective treatments (Winhusen et al., 2007). The scope of the cocaine problem is largely attributed to the advent of crack, an inexpensive, smokable and, thus, particularly addictive form of cocaine, in the mid-1980s. In 2009, 1.1 million people in the United States were abusing or dependent on cocaine (SAMHSA, 2010). In Europe, cocaine use rates have increased significantly in recent years with cocaine use rates of 2 million in 1998 increasing to 4.1 million in 2008 (UNODC, 2010). Because psychosocial interventions are associated with high relapse rates, an impressive amount of resources have been devoted to finding pharmacological treatments that could be used in conjunction with psychosocial treatments; yet there still is no widely used, safe and effective treatment for cocaine dependence (Kuehn, 2009). Identifying and/or developing an effective pharmacological treatment for cocaine dependence is a critical goal for NIDA. To this end, the NIDA Addiction Treatment Discovery Program (ATDP) evaluates compounds at a number of academic and industrial sites under contract to NIDA, and analyzes the resulting preclinical data for potential efficacy and possible advancement of compounds to safety testing and clinical trials. Compounds are obtained by the ATDP from industry, academic, and commercial sources, and are provided to contract sites under blinded conditions to be evaluated in standard protocols developed for the express purpose of identifying potential medications for substance abuse disorders. In this context, Nancy Mello, Ph.D., and her colleagues at McLean Hospital, Harvard University, under NIDA contract N01DA-8-8876, have developed a primate cocaine self-administration protocol for use in evaluating the potential efficacy of specific compounds selected by the ATDP. This contract protocol has been used by the NIDA ATDP for 16 years to evaluate the potential efficacy of medications for the treatment of cocaine dependence.

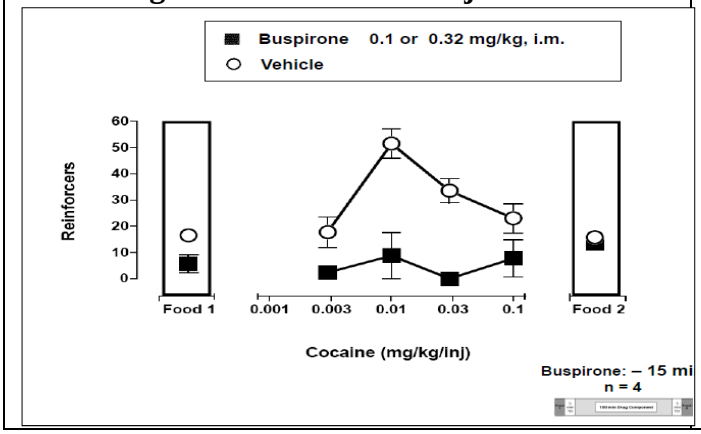
The NIDA contract protocol used by Mello and colleagues entails training rhesus monkeys to lever-press to deliver intravenous (IV) infusions of cocaine using a fixed-ratio (FR) schedule that is gradually increased to FR30. The same monkeys are also trained to lever-press to receive banana pellets before and after the session in which cocaine is available. After initial dose-range testing with a medication, the entire dose-effect curve of cocaine is examined using one dose of the study medication. In the Mello protocol, a positive result is a downward shift in the cocaine dose-effect curve (i.e., the monkeys evidence a decrease in lever-presses across multiple cocaine doses) with no effect on food responding. Other possible medication effects include a rightward shift in the cocaine effect curve, which would indicate that the medication is decreasing the reinforcing effects of cocaine or a leftward shift in the curve, which would indicate that the medication is increasing the reinforcing effects of cocaine (Mello and Negus, 1996). The Mello protocol has several key strengths. First, it includes an intrinsic control for non-specific effects on lever pressing which are at the root of many of the false positive results described in the published research literature. Specifically, the food-administration session conducted after administration of the test compound and both before and after the availability of cocaine provides control data from the same subjects in the same session. A second major strength is the examination of the entire dose-effect curve of cocaine, which avoids misleading "reductions" in self-administration that are artifacts of increased cocaine potency, reflected by leftward shifts in the cocaine dose-effect curve. A final key strength lies in the fact that in 16 years of use, the Mello protocol has yielded positive results for only five of approximately 81 compounds tested, suggesting that the protocol likely has a low false-positive rate. Most of the data generated by the Mello protocol have not been published because the majority of the compounds evaluated were proprietary. Four of the compounds producing positive results cannot be tested in the clinic due to various safety issues. The data from the fifth compound, buspirone, is provided in section 4.2.

4.2 NIDA Unpublished Data for Buspirone

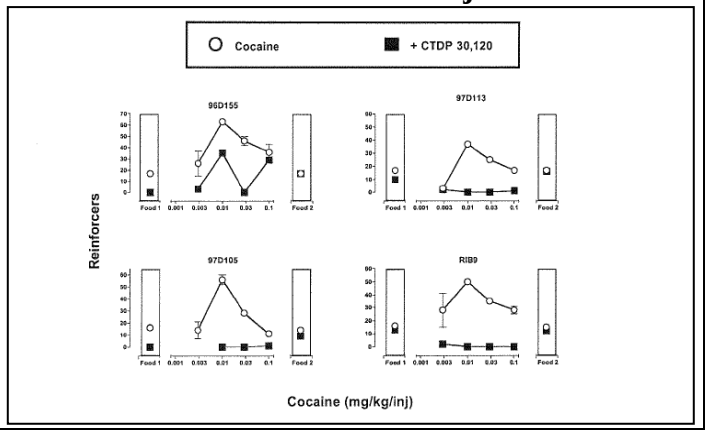
Buspirone was FDA-approved for the treatment of generalized anxiety disorder in 1986, has little abuse potential (Lader, 1991), and a well-known safety profile (Julien, 2005). NIDA has unpublished data on buspirone from several labs. As mentioned above, buspirone is one of only five compounds to have yielded positive results when used in the Mello protocol. The data from that protocol are displayed in Figure 2, with 2a providing the averaged data and 2b providing the data from the four individual rhesus monkeys studied. As can be seen in 2a, buspirone, relative to saline, decreased cocaine self-administration across multiple doses with only minor effects on food responding. As can be seen in Figure 2b, reduction of cocaine self-administration was seen in all four monkeys. The rarity of this result, in combination with the safety and clinical availability of buspirone, has led NIDA to conclude that buspirone merits clinical evaluation.

Figure 2: Primate cocaine self-administration as a function of medication and cocaine dose (Data generated under NIDA contract N01DA-8-8876 to McLean Hospital, Nancy Mello, Ph.D.)

2a. Averaged data from four subjects



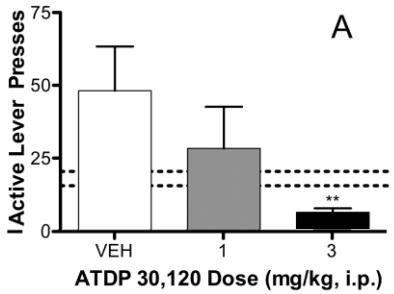
2b. Individual data from four subjects



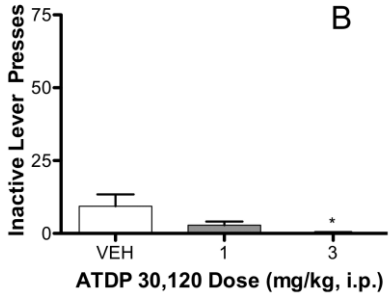
In addition to the results yielded by the Mello protocol, NIDA has other unpublished data suggesting the potential efficacy of buspirone as a cocaine-dependence treatment. Specifically, buspirone has been found to reduce footshock-induced cocaine reinstatement in an animal model of stress-induced relapse (see Figure 3), and was also effective in blocking cue- and priming-induced relapse to methamphetamine self-administration in rats (Data generated under NIDA contract N01DA-8-8889). These rodent models are widely used and have good face validity in that the "triggers" for relapse used in these studies are the same as those reported by humans that relapse. These triggers are 1) exposure to a stressor (such as loss of job), 2) exposure to the environmental cues associated with drug use (people, places and things), or 3) the "sampling" or priming produced by a "taste" of the drug of abuse.

Figure 3. A. Lever presses on the previously active lever following footshock as a function of buspirone (ATDP 30,120). B. Responding on the inactive lever. (Data generated under NIDA contract N01DA-8-8889 to MCV, Patrick Beardsley, Ph.D.).

3a. Lever presses on previously active lever



3b. Responses on the inactive lever



Finally, in vitro data suggest that the behavioral effects of buspirone might be mediated by interactions with dopamine (DA) D_3 or D_4 receptors, rather than $5HT_{1A}$ receptor activation. Table 1 provides data on buspirone's binding and agonist/antagonist potency for $5HT_{1A,}$ $D_{2,}$ $D_{3,}$ and D_4. This is interesting in that pre-clinical research has found that DA D_3 receptor antagonists reduce both the effects of cocaine and cocaine reinstatement (Vorel et al., 2002; Xi et al., 2006; Heidbreder and Newman, 2010). In a review of DA D_3 antagonists' potential in treating addiction, Heidbreder and Newman (2010) note that, while there is insufficient evidence to suggest that these agents would be effective in stopping on-going use, there is evidence to suggest that they may be effective in relapse-prevention for recently abstinent substance-dependent individuals. Identifying an effective relapse-prevention medication for cocaine dependence would be extremely beneficial in that relapse rates are substantial (Simpson et al., 1999). The high relapse rates following discharge from inpatient settings is well documented, with studies of shorter stays (2-10 days) reporting relapse rates of 72% within 4 weeks (Back et al., 2010) and 86% within 12 weeks (Schmitz et al., 2001). Studies of longer inpatient/residential stays (2-4 weeks) have reported relapse rates of 65% (Sinha et al., 2006) and 72% (Paliwal et al., 2008; Hyman et al., 2008) within 90 days following discharge. It should be noted, however, because of buspirone's lack of pharmacological selectivity, it will be impossible to relate behavioral effects to actions at one receptor but, notwithstanding the inability to test a pharmacology hypothesis, the clinical evaluation of buspirone will provide important evidence regarding the predictive validity of the Mello protocol.

Table 1: Buspirone receptor binding and agonist/antagonist potency

Measure (nM)	Kula et al (1994)	Tallman et al (1997)	Toll[a]	Janowsky[b]	Sibley[c]
5H1a Ki			15	33.2	
5HT1a fx EC50				106.33	
D2 Ki	260		63	22.2	230
D2 fx IC50				34	1000
D3 Ki	3.5		35	7	93.5
D3 fx IC50			8.7	44.9	212.6
D4 Ki		136		93	9.06
D4 Fx				62	

[a] Data generated under NIDA contract N01DA-7-8072 to SRI, Larry Toll, Ph.D.,
[b] Data generated under NIDA contract IAG Y1-DA0101-02 to the PVAMC, Aaron Janowsky, Ph.D.
[c] David Sibley, personal communication 2011

4.3 Published Pre-clinical Data for Buspirone

Published pre-clinical research evaluating the possible efficacy of buspirone as a treatment for cocaine dependence has produced mixed findings. Gold and Balster (1992) reported that acute doses of buspirone (0.1 and 0.3 mg/kg, IV) altered cocaine self-administration in rhesus monkeys but that these effects were attenuated during more chronic dosing. Callahan and Cunningham (1997) reported that buspirone (2.5-20 mg/kg intraperitoneal (IP)) dose-dependently reduced the discriminative stimulus properties of cocaine in rats, which they suggested might be due to its DA antagonist properties. In contrast, Rapoza (1993) reported that buspirone (2.0 - 16 mg/kg IP) did not significantly reduce the discriminative stimulus properties of cocaine in rats. In addition, Ali and Kelly (1997) reported that buspirone (0.5 - 2.0 mg/kg IP) did not significantly impact cocaine conditioned place preference in mice. Ettenberg and Bernardi (2007) reported that buspirone (2.5 mg/kg IP) did not reduce the immediate positive effects of cocaine but significantly reduced the negative effects and, in another study, found that buspirone at the two highest doses tested (2.5 and 5.0 mg/kg IP) decreased the aversion-induced avoidance of cocaine (Ettenberg and Bernardi 2006). In addition, Aceto and Bowman (1993) reported that buspirone (0.2, 0.4, 0.8 mg/kg) significantly decreased adverse effects of cocaine in rats and rhesus monkeys. In contrast, Paine et al. (2002) reported that buspirone (0.5 or 1.0 mg/kg IP) did not significantly decrease cocaine-induced anxiety in rats. Finally, Homberg et al (2004) reported that buspirone (1.25, 2.5 mg/kg IP) reduced progressive ratio cocaine self-administration in rats more prone to self-administration (high grooming rats) while failing to decrease cocaine self-

administration in rats less prone to self-administration (low grooming rats), suggesting that individual differences may play an important role in medication response. It is important to note that there are no published pre-clinical data evaluating buspirone as a potential relapse-prevention treatment. However, NIDA's three reinstatement studies of buspirone suggest that it would be an effective relapse prevention agent, consistent with D3 antagonist effects as reviewed by Heidbreder and Newman (2010).

4.4 Buspirone Clinical Trials in Substance Abusing Populations

Buspirone is FDA-approved for the treatment of generalized anxiety disorder and, thus, several of the studies of buspirone in substance abusing populations have been conducted with individuals suffering from both anxiety and a substance use disorder (SUD). Specifically, several investigators have studied the efficacy of buspirone in treating anxious alcohol-dependent individuals including Kranzler et al. (1994), Malcolm et al. (1992), and Tollefson et al., (1992). Kranzler et al. (1994) reported that buspirone, relative to placebo, increased retention, decreased anxiety, and delayed time to first heavy drinking day in anxious alcohol-dependent participants who had been abstinent for at least one week prior to randomization. In contrast, Malcolm et al. (1992) reported no significant benefit of buspirone, relative to placebo, on any measures of alcohol use or anxiety in anxious alcohol-dependent veterans randomized during inpatient/residential SUD treatment and followed up in outpatient treatment. Tollefson et al., (1992) reported that buspirone, relative to placebo, significantly reduced desire for alcohol, decreased anxiety and increased treatment retention in anxious alcohol-dependent/abusing participants who had recently been discharged from inpatient SUD treatment and who had been abstinent from alcohol for 30 -90 days. A randomized controlled trial of buspirone for treating anxiety in methadone-maintained opioid-dependent individuals found that buspirone did not significantly decrease anxiety but was associated with a trend towards slower return to illicit substance use in a subgroup of compliant participants (McRae et al., 2004).

Other investigators have evaluated the efficacy of buspirone in treating substance abusers not selected on anxiety. Bruno (1989) reported that buspirone, relative to placebo, significantly decreased craving and anxiety and significantly increased retention and improved alcohol use outcomes in alcohol abusers who were actively using at time of randomization. Malec et al. (1996) reported no significant benefit of buspirone, relative to placebo, in alcohol or anxiety outcomes in alcohol-dependent participants who expressed a desire to reduce use of, or be abstinent from, alcohol. An open-label trial of buspirone for marijuana-dependent individuals with on-going use reported reductions in marijuana use and craving (McRae et al., 2006). Finally, a randomized controlled trial of buspirone for marijuana dependence in ongoing users found a trend for a greater percentage of negative urine drug screens in the buspirone, relative to the placebo, group, which reached significance in the analysis of study completers (McRae-Clark et al., 2009). From an efficacy standpoint, the clinical trials of buspirone in substance abusing populations have produced mixed results. Of note from a safety standpoint, these trials have reported that the participants have generally tolerated buspirone well.

4.5 Clinical Trials of Buspirone in Cocaine-Dependent Populations

A review of the literature reveals two studies of buspirone in human cocaine abusers. First, Giannini et al. (1993) evaluated its efficacy relative to placebo in reducing symptoms of withdrawal in 32 chronic cocaine abusers and 24 chronic PCP abusers in a 30-day outpatient study. They reported that buspirone, compared to placebo, significantly reduced cocaine withdrawal symptoms, as measured by the Brief Psychiatric Rating Scale, starting at day five with increasing effects observed through day 30; in contrast, a significant buspirone effect for PCP withdrawal was not seen until day 30.

The other buspirone clinical trial data come from Moeller et al. (2001) who evaluated the association between impulsivity, severity of cocaine use, and treatment outcomes in a small (n=35) 12-week double-

blind, placebo-controlled trial of buspirone with group therapy. They reported no significant buspirone effect on cocaine use, cocaine craving, and retention, which they noted could reflect a Type-II error given the small sample size. The failure to find a buspirone effect for cocaine use is not surprising given that the current hypothesis, based on D_3 antagonist pre-clinical data as well as NIDA unpublished data specifically on buspirone, is that buspirone will be effective in relapse-prevention but may not be effective in reducing use in active users such as those included in the Moeller et al. (2001) study. It should be noted that, based on the means and standard deviations reported by Moeller et al. (2001) for endpoint craving, buspirone's effect size (D = .75; Cohen, 1988) was in the medium to large range. Moreover, based on the means and standard deviations reported by Moeller et al. (2001) for the number of treatment weeks attended, buspirone's effect size (D = .73; Cohen, 1988) was in the medium to large range. From a relapse prevention perspective, a medication that significantly decreases craving and increases treatment attendance might have utility as a cocaine dependence treatment.

4.6 Mechanisms by which Buspirone Could Prevent Relapse

Factors that could mediate buspirone's efficacy as a relapse-prevention treatment are those related to cocaine relapse/use that could be affected by buspirone. Factors meeting these criteria include drug attentional bias, compulsivity, and craving. Having a greater understanding of the mechanisms by which buspirone exerts its effect could facilitate future medication development efforts and, thus, these potential mechanisms of action will be evaluated in the present study.

4.6.1 Drug Attentional Bias

The incentive salience hypothesis postulates that the pathological wanting of the drug, which is distinct from drug liking, is what drives the compulsive use that marks addiction (Robinson & Berridge, 1993; Robinson & Berridge, 2008; Berridge et al., 2009). This pathological wanting leads to the nearly sole focus on substance use seen in addiction (DSM-IV-TR, American Psychiatric Association, 2000), is particularly triggered by exposure to drug-related cues (Everitt et al., 2008), and is associated with a broad range of brain regions (Berridge et al., 2009). One measure of the increased salience of drug cues is the drug-word Stroop task that assesses attentional bias for drug cues (Carpenter et al., 2006; Vadhan et al., 2007). Increased attentional bias for drug cues, as measured by the drug-word Stroop, has been found to be significantly greater in stimulant-dependent, relative to normal control, participants (Ersche et al., 2010) and to be associated with poorer treatment outcomes in cocaine-dependent individuals (Carpenter et al., 2006). Past research has found that DA antagonists can improve performance on the Drug Stroop in heroin-dependent individuals (Franken et al., 2004), and that a DA agonist worsened Drug Stroop performance in highly compulsive stimulant-dependent individuals while improving performance in low compulsive stimulant-dependent individuals (Ersche et al., 2010). As a dopamine antagonist, buspirone could be expected to decrease drug attentional bias, which, in turn, could reduce the likelihood of relapse.

4.6.2 Drug Compulsivity

Compulsive drug use is a defining characteristic of addiction (Baler and Volkow, 2006). Ersche et al (2010) recently reported that the impact of dopaminergic agents in stimulant-dependent participants differed as a function of compulsivity, measured by the Obsessive Compulsive Drug Use Scale (Franken et al., 2000; Franken et al., 2002), and noted that research evaluating dopaminergic agents should include a measure of compulsivity. The inclusion of a measure of drug compulsivity in the present trial is further supported by evidence that buspirone might be effective in decreasing compulsive behaviors. Specifically, a double blind randomized trial of buspirone and clompiramine in individuals with obsessive-compulsive disorder found that buspirone significantly decreased compulsivity as measured by the Yale-Brown Obsessive Compulsive scale (Pato et al., 1991). Assessing compulsivity in the present trial is thus important in that buspirone might directly decrease compulsivity, which in turn could impact cocaine relapse/use, or, as noted by Ersche et al

(2010), dopaminergic agents might have differential effects on stimulant-dependent individuals depending on level of compulsivity and, thus, should be considered when evaluating dopaminergic agents.

4.6.3 Craving

It has been hypothesized that craving can lead to cocaine use but a significant relationship between craving and use has not been found consistently (Paliwal et al., 2008; Preston et al., 2009). The failure to find a consistent relationship has been attributed to several factors, primarily related to measurement issues (Preston et al., 2009), including the failure to capture the multidimensional aspect of craving (Paliwal et al., 2008). It has also been noted that the relationship between craving and cocaine use can depend upon the individual's ability to resist the urge to use and that an effective treatment might weaken the relationship between craving and use by increasing a patient's ability to resist using (Weiss et al., 2003). The Cocaine Craving Questionnaire-Brief (CCQ-Brief; Sussner et al., 2006), which captures the multidimensional nature of craving including perceived ability to resist using, has been found to be predictive of time to cocaine relapse following inpatient treatment (Paliwal et al., 2008). Evidence to suggest that buspirone may be effective in reducing craving comes from two randomized placebo controlled trials finding that busprione significantly decreased craving in alcohol abusing/dependent individuals (Bruno et al., 1989; Tollefson et al., 1992) and an open-label study finding that buspirone reduced craving in marijuana dependent individuals (McRae et al., 2006). However, double-blind placebo controlled trials in marijuana-dependent (McRae-Clark et al., 2009) and alcohol-dependent (Malcolm et al., 1992; Malec et al., 1996) individuals failed to find a significant effect of buspirone on craving. As noted in section 4.5, Moeller et al. (2001) reported no significant effect for buspirone on cocaine craving. However, based on the means and standard deviations reported for endpoint craving (Moeller et al., 2001), buspirone's effect size (D=.75; Cohen, 1988) was in the medium to large range.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

1. To evaluate the efficacy of buspirone, relative to placebo, in preventing relapse in cocaine-dependent adults in inpatient/residential treatment who are planning to enter outpatient treatment upon inpatient/residential discharge.

5.2 Secondary Objectives

1. To evaluate the impact of buspirone, relative to placebo, on other drug-abuse outcomes in cocaine-dependent adults in inpatient/residential treatment who are planning to enter outpatient treatment upon inpatient/residential discharge.

2. To evaluate the impact of buspirone, relative to placebo, on factors that may mediate buspirone's efficacy as a relapse-prevention treatment in cocaine-dependent adults in inpatient/residential treatment who are planning to enter outpatient treatment upon inpatient/residential discharge.

6.0 STUDY DESIGN

6.1 Overview of Two-Stage Study Design

Buspirone has not been previously evaluated as a relapse-prevention treatment for cocaine dependence and, thus, there is little empirical data upon which to base the design of a full-scale clinical trial. The present protocol is thus designed as a two-stage process in which a pilot study will first be completed to obtain information needed to design the full-scale clinical trial (e.g., information about medication tolerability, adherence, missing data rates, etc.). The pilot and full-scale trials will utilize similar treatment phases and outcomes with adjustments made as needed (e.g., to medication dosing, sample size estimates, etc.) to the full-scale trial based on the pilot data. Both trials will be a 16-week, intent-to-treat, double-blind, placebo-controlled, randomized trial. Eligible participants will be randomized to buspirone or matching placebo and will be scheduled to attend two research visits per week throughout the active treatment phase which begins with randomization and ends on day 7 of study week 15. A single visit will be scheduled in week 16 to complete retrospective data for week 15. Participants will be screened after being admitted to inpatient/residential treatment and will be randomized when they have approximately 12-19 days remaining of their scheduled inpatient/residential stay, allowing the 10-day dose escalation period to be completed in the inpatient/residential setting. Participants will receive buspirone or placebo throughout the 15-week active treatment phase. Randomization strata include study site and cocaine use frequency (<10 days or ≥ 10 days in the 28 days prior to inpatient/residential admission).

The primary outcome measure is the maximum days of continuous cocaine abstinence, as assessed by twice-weekly UDS and self-report, during study weeks 4-15 (see section 6.5.1 for details). Secondary outcomes include time to first cocaine use following inpatient/ residential discharge, cocaine-free and drug-free weeks assessed by self-report and UDS, cocaine-use and substance-use days as assessed by self-report, cocaine binging, HIV risk behavior, quality of life, and substance-abuse treatment attendance. Process variables include drug attentional bias, compulsivity, and craving. Safety measures include vitals, adverse events (AEs), and mood measures.

Patients who are in an inpatient/residential treatment program with an expected stay of 14-28 days, plan to attend outpatient treatment following discharge through the end of the active treatment phase, and are likely to meet DSM-IV-TR criteria for cocaine dependence and other study requirements will be recruited for the study. Participants may be recruited from a variety of other sources as well, including advertising. The site's Institutional Review Board (IRB) will approve recruitment advertisements and methods (such as print, Facebook, Craigslist, etc). An attempt will be made to include approximately 50% female participants in the study sample. In addition, efforts will be made to recruit a study sample that reflects, or exceeds, the proportion of minorities in the community where the site is located.

6.2 Pilot Study Design

The overall design of the pilot study is described in section 6.1 with factors specific to the pilot study described in the present section. Approximately 60 participants, recruited by approximately six sites, will be randomized into the pilot study. Site staff participating in recent CTN trials recruiting cocaine-dependent individuals, including CTN-0037 and CTN-0046, have reported a decrease in the number of cocaine-dependent patients seeking treatment, with increases in the number of opioid and alcohol dependent clients entering treatment. Based on this experience, it is estimated that study sites will, on average, be able to randomize 1.6 participants per month per site. Based on this randomization rate, enrollment is expected to take place over a period of approximately 6-7 months once all sites are initiated.

All of the outcome measures listed in section 6.1 will be obtained in the pilot trial but data analysis will be completed in two phases, with the first phase focusing on the data needed for planning the full-scale trial

(e.g., information about feasibility, primary outcome, medication tolerability and adherence, TAU characteristics at each site, etc.) and the second including an analysis of the remaining data. This staged approach to data analysis will serve to minimize the time between the end of data collection for the pilot study and initiation of the full-scale trial.

6.3 Full-Scale Study Design

The overall design of the full-scale study is described in section 6.1. The number of participants for the full-scale trial will be determined based on data from the pilot trial but is estimated to be approximately 264 randomized participants. The results from the pilot study will be used to modify the design, procedures, medication dosing, and analytic plan of the full-trial as needed.

6.4 Site and Participant Selection

6.4.1 Site Selection

6.4.1.1 Site Characteristics

Participating sites must:

1. have access to a medical clinician (e.g., P.A., M.D., D.O., N.P.) or R.N. to perform medical assessments (e.g., medical history, concomitant medications, etc.). The site must have access to a study physician (an M.D or D.O.) who will review laboratory results, determine participant's medical eligibility prior to randomization, and will review adverse events. A medical clinician or study physician (degree and licensing requirements depend on the regulations of the state in which the site is located) will regulate the medication dose appropriately, and advise about possible untoward interactions between the study medications and other medications the study participant may be taking.

2. have access to, or the ability to contract with, a pharmacy/pharmacist (or other appropriately qualified entity based on local/state regulations) to store/dispense study medications

3. be able to provide after-hours clinical back-up for study-related emergencies

4. have access to, or the ability to contract with, a phlebotomist or other appropriate professional, to complete blood draws

5. have an inpatient/residential treatment program with a 14-30 day average length of stay with a local outpatient program that provides treatment post-discharge, which can include continuing care. Inpatient/residential treatment programs that have an established referral relationship with a local outpatient program may also be eligible.

6. admit a sufficient number of cocaine-dependent individuals to inpatient/residential treatment such that a rate of at least 1.6 randomizations per month will be feasible.

6.4.1.2 Rationale for Site Selection

The site eligibility criteria outlined in section 6.4.1.1 consist of the minimal staffing that is required in order to safely and effectively conduct a medication trial. Since the design of the present trial requires inpatient/residential treatment with follow-up care in an outpatient program only sites that have this combination of programs are eligible to participate.

6.4.2 Participant Selection

6.4.2.1 Inclusion Criteria

Potential participants must:

1. be 18 years of age or older

2. be able to understand the study, and having understood, provide written informed consent in English

3. meet DSM-IV-TR diagnostic criteria for current (within the last 12 months) dependence for cocaine, must self-report being primarily a crack cocaine user, having used crack cocaine a minimum of four times in the 28 days prior to inpatient/residential admission, and must report that their typical pattern of use is at least once a week

4. have a willingness to comply with all study procedures and medication instructions

5. be enrolled in an inpatient/residential program at a participating CTP, scheduled to be in inpatient/residential treatment for approximately 12-19 days when randomized, and planning to enroll in local outpatient treatment through the end of the active treatment phase (i.e., study week 15)

6. if female and of child bearing potential, agree to use one of the following methods of birth control:
    - oral contraceptives
    - contraceptive patch
    - barrier (diaphragm or condom)
    - intrauterine contraceptive system
    - levonorgestrel implant
    - medroxyprogesterone acetate contraceptive injection
    - complete abstinence from sexual intercourse
    - hormonal vaginal contraceptive ring

6.4.2.2 Exclusion Criteria

Potential participants must not:

1. meet DSM-IV-TR diagnostic criteria for current (within the last 12 months) opioid dependence

2. have a medical or psychiatric condition that, in the judgment of the study physician, would make study participation unsafe or which would make treatment compliance difficult. Medical conditions that may compromise participant safety or study conduct include, but are not limited to:
    - AIDS according to the current CDC criteria for AIDS
    - liver function tests greater than 3X upper limit of normal
    - serum creatinine greater than 2 mg/dL

3. have a psychiatric disorder requiring continued treatment with a pychotropic medication

4. have a known or suspected hypersensitivity to buspirone

5. be pregnant or breastfeeding

6. have used any of the following medications within 14 days of randomization: monoamine oxidase (MAO) inhibitors such as phenelzine (Nardil), selegiline (Eldepryl), isocarboxazid (Marplan), or tranylcypromine (Parnate)

7. be taking any medications which, in the judgment of the study physician, may produce interactions with buspirone that are sufficiently dangerous so as to exclude the patient from participating in the study. Alternatively, the study physician, in consultation with the patient and his or her physician, may elect to withdraw the patient from the problem medications before randomization. Some of the possible interactions are discussed in section 8.8.

8. be anyone who, in the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.)

9. be a significant suicidal/homicidal risk

6.4.2.3 Rationale for Eligibility Criteria: Table 2

Table 2: Rationale for Study Eligibility Criteria

Criterion#	Criterion Description	Criterion Rationale
I1	18 years of age or older	Definition of Study Sample (adults)
I2	Understand study/give consent	GCP Requirement
I3	DSM-IV-TR Diagnosis of cocaine dependence/recent use	Definition of Study Sample (cocaine dependent)
I4	Willing to comply with study procedures	To help ensure that the participant will provide useful data
I5	Enrolled in inpatient/residential treatment program	Required by study design (i.e., to test relapse prevention)
I6	Agree to birth-control	Safety of buspirone during pregnancy has not been established
E1	Current opiate dependence	To reduce sample heterogeneity
E2	Psychiatric condition making participation unsafe/difficult	Safety and to help ensure that the participant will provide useful data
E3	Require psychotropic medication	Could interfere with efficacy evaluation or potential interaction with buspirone
E4	Hypersensitivity to buspirone	Safety
E5	Pregnancy or lactation	Safety during pregnancy not established; buspirone/metabolites expressed in breast milk
E6	MAOI within 14 days of randomization	Safety – MAOIs can cause severe increases in blood pressure when used with buspirone
E7	Taking medications with possible buspirone interactions	Safety
E8	Unlikely to complete the study	To help ensure that the participant will provide useful data
E9	Significant Suicide/Homicide risk	Safety

6.5 Outcome Measures

6.5.1 Primary Outcome Measure-Maximum Days of Continuous Cocaine Abstinence

There is no agreed-upon operational definition of cocaine relapse (Schmitz et al., 2001) and, thus, no standard measure upon which to base the primary outcome measure for the present protocol. As noted by Havassy et al. (1993), defining relapse as any use is appealing in that it is relatively easy to measure and unambiguous to interpret (i.e., use did or did not occur) but is problematic in that a single use may be an overly conservative definition in that one use may not predict continued use. Indeed, this potential downside was found in a cocaine relapse prevention trial completed by Schmitz et al. (2001) in which no medication effect was found for time to first use while a significant Medication x Time x Therapy effect was found for percentage of cocaine-negative urines, which reflected a treatment difference during the final weeks of the 12-week treatment phase. Jones et al. (2004) evaluated tryptophan plus vouchers for cocaine dependent patients who were stabilized in residential treatment for 4-9 days followed by a 16 week outpatient period, with treatment (i.e., vouchers and full medication dose) provided during the first 12 outpatient weeks. A key outcome measure of the trial was continuous cocaine abstinence during the 12-week outpatient treatment period for which a significant main effect of vouchers was found, suggesting that this measure is sensitive to treatment effects.

The primary outcome measure selected for the present two-stage protocol is the maximum days of continuous cocaine abstinence during study weeks 4-15. Cocaine use will be determined by a combination of self-report and qualitative UDS assessments as outlined in section 9.4.2 and described in detail in the protocol's Statistical Analysis Plan (SAP). The Timeline Follow-back (TLFB) procedure (Sobell and Sobell, 1992; Fals-Stewart, 2000) will be used to assess the participants' self-reported use of substances for each day of the study. A rapid UDS system that screens for drugs of abuse including cocaine, methamphetamine, amphetamine, opioids, benzodiazepines, marijuana, barbiturates, methadone, oxycodone, and methylenedioxymethamphetamine (MDMA, Ecstasy) will be used to analyze the urine samples. Urine samples will be collected using temperature monitoring and the validity of urine samples will be checked with the use of a commercially available adulterant test. In cases where the temperature reading/adulterant test indicates a non-valid sample, an attempt will be made to obtain a second urine sample.

6.5.2 Secondary Outcome Measures

The impact of buspirone, relative to placebo, on drug-abuse outcomes will be evaluated with the secondary measures listed below. These assessments include measures of reduction in drug use (e.g., cocaine-use and substance-use days, cocaine binging) and in adverse consequences related to drug use (e.g., ASI-Lite, Risk Assessment Battery, Quality of Life).

1. Time to First Cocaine Use

The occurrence of cocaine use will be determined by a combination of self-report and qualitative UDS. Since cocaine use is significantly less likely to occur when a participant is in an inpatient/residential setting, relative to being outpatient, the length of time during which the participant is at greater risk for use will be accounted for by defining time to first cocaine use as the number of days between inpatient/residential discharge and the first date on which cocaine use occurred.

2. Cocaine-free and Drug-Free Weeks

The percentage of cocaine-free weeks outcome is whether (yes/no) a participant is cocaine-free during study weeks 4-15, as assessed by qualitative UDS and TLFB. At the group level, this outcome translates into the

percentage of participants in each study arm who are cocaine-free during each week of study weeks 4-15. A cocaine-free week is defined as a week in which both urine samples test negative for cocaine and the participant self-reports no cocaine use. A cocaine-positive week is defined as a week in which at least one urine sample tests positive for cocaine or during which the participant self-reports cocaine use. The percentage of drug-free weeks outcome is similar to cocaine-free weeks but rather than being restricted to cocaine, it includes alcohol and other drugs of abuse.

3. Cocaine-use and Substance-use Days

The number of cocaine-use days and the number of substance-use (i.e., alcohol and/or illicit use) days will be obtained from the TLFB (see above). Substance-use days is a key outcome in that abstinence from all substances, including alcohol, is the treatment goal for many CTPs and, thus, it is important to assess the degree to which participants achieve this abstinence goal.

4. Cocaine Binging

In their trial of buspirone for anxious, alcohol-dependent individuals, Kranzler et al. (1994) reported that buspirone did not impact time to first alcohol use but, rather, time to first heavy drinking day. Due to the short half-life of cocaine, it is common for users to binge once they start using. Buspirone's potential impact on reducing cocaine binging, including the amount of cocaine used and the time devoted to using, would not be captured by the standard TLFB procedure which typically assesses the frequency of use. Thus, the amount of cocaine used, and the length of time spent using, will also be assessed.

5. Substance-abuse Treatment Attendance

Several trials evaluating buspirone for alcohol abuse/dependence reported that buspirone, relative to placebo, increased treatment retention (Bruno, 1989; Tollefson et al., 1992 Kranzler et al., 1994). As noted in section 4.5, Moeller et al. (2001) reported no significant effect of buspirone on treatment attendance. However, based on the means and standard deviations reported for number of treatment weeks attended (Moeller et al., 2001), buspirone's effect size (D=.73; Cohen, 1988) was in the medium to large range. In the present trial, participant compliance with substance-abuse treatment attendance will be evaluated by assessing the ratio of the number of treatment hours attended to the number of hours scheduled. Attendance of the research assessment visits will not be scored as substance-abuse treatment attendance. Determination of attendance will be based on the clinic's records of treatment attendance.

6. ASI-Lite

The ASI-Lite is derived from the Fifth Edition of the ASI (McLellan et al., 1992), a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. The CTN ASI-Lite will be completed according to the schedule outlined in Table 3.

7. Risk Assessment Battery (RAB)

Multiple studies have established an association between stimulant use and increased sexual risk behavior (Booth et al., 2000; Lejuez et al., 2005; McCoy et al., 2004). Effective drug-abuse treatment, which decreases stimulant use, decreases sexual risk behavior (National Institute on Drug Abuse, 2006). The Risk Assessment Battery (RAB) (Navaline et al., 1994) is a self-administered assessment of the participant's engagement in activities that increase the likelihood of contracting HIV. Several scores including drug risk, sex risk, total risk, and scale score can be derived from the RAB. The RAB will be completed according to the schedule outlined in Table 3.

8. Quality of Life

The CTN TEAM task force noted that effective substance abuse treatment should improve patients' quality of life in addition to decreasing substance use and recommended that the World Health Organization Quality of Life-BREF (WHOQOL-BREF; WHOQOL Group, 1998) be included in all CTN clinical trials. The WHOQOL-BREF provides a score for four domains: physical health, psychological, social relationship, and environment. This assessment will be completed according to the schedule outlined in Table 3.

6.5.3 Process Measures

1. Drug Stroop

The computerized Drug Stroop developed and validated by Carpenter and colleagues (Carpenter et al., 2006; Vadhan et al., 2007) will be utilized. This assessment includes a total of 100 words, with 20 words associated with cocaine, heroin, and marijuana use, respectively, as well as 20 words associated with multiple substances (e.g., high, sniff, rush, etc.) and 20 neutral words. The cocaine interference score, calculated by taking the difference in reaction times to the cocaine and neutral words, is the primary measure of interest but the other interference scores (e.g., for marijuana, heroin, and mixed) will be calculated as well. The drug Stroop will be completed according to the schedule outlined in Table 3.

2. Obsessive Compulsive Drug Use Scale (OCDUS)

Drug compulsivity will be assessed with the Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al., 2000; Franken et al., 2002), which is a 13 item self-report measure evaluating the strength of compulsions to use cocaine. The total OCDUS score is the primary measure of interest. The OCDUS will be completed according to the schedule outlined in Table 3.

3. Cocaine Craving Questionnaire-Brief (CCQ-Brief)

The Cocaine Craving Questionnaire-Brief (CCQ-Brief; Sussner et al., 2006), which captures the multidimensional nature of craving including perceived ability to resist using, has been found to be predictive of time to cocaine relapse following inpatient treatment (Paliwal et al., 2008). The CCQ-Brief, a 10 item self-report measure, will be completed according to the schedule outlined in Table 3. The CCQ-Brief total score is the primary measure of interest.

6.5.4 Safety Measures

1. Adverse Events (AEs)

AEs will be assessed by study staff as outlined in Table 3. If an AE requires medical attention, it should be reported to a study medical clinician immediately.

2. The Hospital Anxiety and Depression Scale (HADS)

While buspirone is FDA-approved for the treatment of generalized anxiety disorder, several trials conducted with substance abusing samples have failed to find a significant effect of buspirone on anxiety (McRae et al., 2004; McRae-Clark et al., 2009). Research suggests that negative mood states may increase following cocaine abstinence (Epstein and Preston, 2010) and, thus, mood symptoms will be assessed as a safety measure. Specifically, the HADS, a brief, validated instrument that screens for both depression and anxiety (Bjelland et al. 2002), will be completed following the schedule outlined in Table 3.

3. Pregnancy Test and Birth Control Assessment

A urine pregnancy test designed to measure human chorionic gonodotropin hormone will be completed on study day 1 (prior to randomization) and during study weeks 4, 8, 12, and 15. All female participants will be tested except women who have a documented hysterectomy. During screening/baseline, female participants' use of birth control and breastfeeding status will be assessed.

4. Prior/Concomitant Medications

All medications taken by the participant for the 30 days prior to screening/baseline, during screening/ baseline, and during the active study will be documented on a Prior/Concomitant Medications assessment (see Table 3). Medications taken by the participant while in the study should ideally be pre-approved by the medical clinician whenever possible to avoid interactions with the study drug.

5. Vital Signs and Weight

Vital signs, including blood pressure and heart rate, will be assessed according to the schedule in Table 3. In addition, the participant's weight will be recorded during screening/baseline and at the week-8 and week-15 study visits and the participant's height will be recorded during screening/baseline. A trained staff member will assess vital signs, either manually or by using a digital blood pressure monitor calibrated within the past twelve months and ideally approved by the Lead Investigator. Systolic blood pressures greater than 160 or less than 90 and diastolic greater than 100 and less than 60 should be brought to the attention of the medical clinician for review.

6. Assessment of Suicidal Ideation

Cocaine withdrawal symptoms can include dysphoria and increased suicidal ideation (Kampman et al., 1998). Participants will be assessed for suicidal ideation on a weekly basis.

6.5.5 Other Measures

1. Demographics

This assessment will include questions about the participant's ethnicity, age, and sex.

2. Composite International Diagnostic Interview (CIDI) - Substance Abuse Module (SAM)

The substance use disorder diagnostic criteria did not change between DSM-IV and DSM-IV-TR and, thus, the CIDI-SAM (Cottler et al., 2000), which assesses DSM-IV and ICD-10 substance use diagnostic criteria, and which has been used in several CTN trials, can be utilized. A RA who has been trained in the proper administration of this instrument will administer the alcohol and drug sections of the CIDI-SAM during screening/baseline. In addition, each interviewer will undergo a certification check, in which a CIDI trainer rates the administration of the instrument.

3. Medical History

A study medical clinician, study physician, or R.N. will obtain and record the medical history. Prior to randomization, the study physician will review the participant's medical history; this will include a review of the participant's physical exam completed within the past 30 days. It is expected that the physical exam will typically be completed as part of the site's clinical intake.

4. Thoughts about Abstinence

The Thoughts about Abstinence assessment (Hall et al., 1991), which assesses desire to quit, expected success in quitting and estimated difficulty in avoiding relapse, will be completed for alcohol and illicit drugs following the schedule outlined in Table 3.

5. Medication Adherence

Possible medication adherence assessments include the Medication Events Monitoring System (MEMS) which is a medication bottle with a microchip that records the times and dates of bottle opening, pill counts, and participant self-reported adherence. Each of these measures is associated with specific strengths and weaknesses (Liu et al., 2001). In the present trial, the MEMS, pill count, and participant self-report of medication adherence will be collected as outlined in Table 3. A participant's medication compliance for each study week will be defined as the most conservative estimate yielded from the three measures of medication adherence. In addition, a biological measure of adherence will be obtained for participants in the busprione arm. Specifically, urine samples collected during the treatment period will be shipped to a central lab and the samples from the buspirone group will be assayed for buspirone and/or its metabolite (1-PP) using a liquid chromatography/ mass spectrometry/mass spectrometry method.

6. Medication Tolerability

Several measures of medication tolerability will be obtained including the number of participants: reaching maximum dose, having a sustained dose at maximum, reaching target dose in 10 days, having a permanent dose reduction, and being discontinued from the medication and/or study due to AEs.

7. Blood Chemistries

During screening/baseline, blood will be collected in serum separation evacuated venous blood collection tubes. Quantitative analysis will be performed, which will include the following analytes: glucose, creatinine, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), and blood urea nitrogen (BUN). A prescription topical numbing cream may be offered to all participants prior to the blood draw.

8. Substance Abuse Treatment Status

The Substance Abuse Treatment Status form will be used to assess study candidate's status on study inclusion/exclusion criteria related to substance abuse treatment (e.g., enrolled in inpatient/residential treatment, etc.). In addition, information regarding pressure to attend treatment, which can be related to substance use outcome, will be assessed.

9. Suicidal and Homicidal Screening Form

The Suicide and Homicide Screening Form is a structured, reliable interview modified from the Psychiatric Research Interview for Substance and Mental Disorders- PRISM (Hasin, et al. 1996) and will be completed by study staff during screening/baseline. A qualified mental health professional should assess participants reporting current suicidal/homicidal intent.

10. Cocaine related adverse consequences

There is currently no FDA-approved treatment for cocaine dependence (Kuehn, 2009). Obtaining an FDA-approved treatment will require an effective medication and an appropriate measure with which to document its efficacy. Potential cocaine dependence treatments typically have been evaluated based on their impact on cocaine use as assessed by self-report and/or urine toxicology results. Self-report offers the advantage of

providing fairly complete data in that self-reported use can be assessed for 90 days prior to a given study visit and, thus, assessments from missed study visits can be collected at subsequent visits. The primary disadvantage of self-report is that some participants under-represent their use, even when data are obtained under the most ideal circumstances (all information strictly confidential, even shielded from treating clinicians) with research suggesting that the concordance rate between participant self-report and urine toxicology is approximately 90% at the beginning of a trial but then decreases to approximately 75% by the end of a trial (Somoza et al., 2008).

Urine toxicology offers the advantage of an objective measure of cocaine use but has several disadvantages (Winhusen et al., 2003). Specifically, adequate assessment of cocaine use entails the collection of frequent urine samples in order to avoid undetected new uses of cocaine. The frequency of urine collection in cocaine trials is generally three times per week. This tends to make such studies expensive and may serve to reduce the pool of patients willing to participate in the study and, thus, the generalizability of the study findings. Finally, urine toxicology has the disadvantages of being particularly susceptible to data loss due to missed clinic visits (Lavori et al. 1999), of being prone to patient falsification (Eskridge & Guthrie 1997), and of being objectionable to some study participants and staff.

An alternative to focusing on cocaine use itself would be to evaluate a medication's efficacy in ameliorating the major consequences related to cocaine use. This treatment outcome is consistent with the view expressed by an FDA-representative at the NIDA meeting "Clinically Meaningful Substance Abuse Treatment Outcome Measure for Effectiveness Trials" (Bethesda MD, December 2009), that an individual who uses drugs without consequences can be considered a treatment success. Indeed, such an outcome would be consistent with the concept of cocaine addiction itself, which is not diagnosed by urine toxicology results or self-report of a particular pattern of use but, rather, on the negative impact that cocaine use has on the addicted individual. There are assessments of the negative consequences of alcohol use including the 45-item Drinking Inventory of Consequences (DrInC; Miller et al., 1995) and an abbreviated version of the DrInC, the 15-item Short Index of Problems (SIP: Miller et al., 1995, Feinn et al., 2003). The items for the DrINC were created by a panel of experts and designed to assess five areas: Physical, Intrapersonal, Social Responsibility, Interpersonal, and Impulse Control consequences (Alterman et al., 2009). Alterman et al. (2009) modified the SIP by replacing "drinking" with "drug use" for each SIP item, with the modified assessment called the SIP-D, and reported good internal consistency and concurrent validity for the instrument in a sample of substance-abuse patients in outpatient treatment. The SIP-D will be included in the present evaluation and analyses will be conducted to evaluate its internal consistency and concurrent validity in the present samples of cocaine-dependent individuals. In addition, we will collect reliability and validity data on a new self-report instrument, the cocaine-related adverse consequences (CRAC) questionnaire, which will be designed to assess the major functioning consequences that are slated for inclusion in DSM-V (e.g., failure to fulfill major role obligations; persistent social/ interpersonal problems; great deal of time spent using or recovering from use; giving up important social/ occupation/recreational activities; persistent physical/psychological problems) but which will tailor the questionnaire items specifically to cocaine use.

11. Drop-out Risk Assessment

The Drop-out Risk Assessment form will be used to assess study candidates' status on the exclusion criterion of being unlikely to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.).

12. Fagerström Test for Nicotine Dependence

The results from clinical studies suggest that the rate of smoking in cocaine abusers is 75-80% (Budney et al., 1993; Sees and Clark, 1993; Gorelick et al., 1997) and that smoking cigarettes is associated with more severe addiction, including more frequent cocaine use, a greater likelihood of injecting or smoking cocaine,

and more severe employment and legal difficulties (Roll et al., 1996). The Fagerström Test for Nicotine Dependence is a brief self-administered assessment of cigarette use patterns (Heatherton et al., 1991), which yields a single overall dependence score. It will be completed following the schedule in Table 3.

13. Frontal Systems Behavior Scale (FrSBe)

There is evidence that prefrontal cortex (PFC) dysfunction may be impaired in stimulant-dependent patients (Goldstein and Volkow, 2011) but there are outstanding questions about the degree to which PFC dysfunction is clinically significant in stimulant-dependent patients, related to stimulant use as opposed to being pre-existing, and related to treatment outcomes. The Frontal Systems Behavior Scale (FrSBe) is a brief, reliable and valid assessment of three neurobehavioral domains reflective of PFC functioning (Apathy, Disinhibition, and Executive Dysfunction, summed for a Total), assesses both pre-morbid and post-damage functioning, and has a specific cutoff for defining clinically significant impairment. A recent study used the FrSBe to evaluate PFC dysfunction in 180 patients meeting DSM-IV criteria for methamphetamine- and/or cocaine dependence. The results revealed that the patients evidenced clinically significant PFC dysfunction as measured by the FrSBe, that PFC dysfunction was present prior to the initiation of stimulant abuse, that stimulant use was associated with significant worsening of PFC function, and that clinically significant disinhibtion was associated with poorer treatment outcomes (Winhusen et al., in preparation). The FrSBe is being obtained in the present study to replicate, and expand on, the findings of Winhusen et al. (in preparation). The FrSBe will be completed following the schedule in Table 3.

6.6 Randomization Plan

Eligible participants will be randomized in a 1:1 ratio to the buspirone and placebo arms. The randomization process will be performed by computer at a centralized location. Randomization will be stratified by site and cocaine use frequency (<10 days or ≥ 10 days of use in the 28 days prior to inpatient/residential admission). The block size chosen will be adequate to ensure approximate treatment balance. The number in each treatment group will never differ by more than a factor of KB/2 where B is the block size and K is the number of strata.

6.7 Study Treatments

6.7.1 Buspirone

Participants randomized to buspirone will receive buspirone as described in section 8.0 in addition to the inpatient/residential and outpatient treatment as typically provided by the CTP. As described in section 8.0, participants will receive contingency management to increase medication adherence.

6.7.2 Placebo

Participants randomized to placebo will receive matching placebo as described in section 8.0, in addition to the inpatient/residential and outpatient treatment as typically provided by the CTP. As described in section 8.0, participants will receive contingency management to increase medication adherence.

7.0 STUDY PROCEDURES

7.1 Study Overview

Table 3 provides an overview of the participant procedures and assessments. Ideally, all study procedures and assessments will be completed in person. However, if the participant is not able to come to the site and (s)he agrees, some assessments and/or visits may be conducted by phone, by mail, or at appropriate off-site locations. Alternatively, assessments may be completed on participants' or other off-site computers via secure study website(s) if access to a computer with internet service is available.

7.2 Participant Recruitment and Consent

Potential study candidates may be identified and pre-screened by telephone or face-to-face interview, prior to or after inpatient/residential admission, but consent and subsequent screening will occur after admission. Study candidates who, based on the pre-screen, are likely to be eligible and are interested in the study will be invited to receive an explanation of the study purpose and requirements. If still interested after receiving a face-to-face description of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form.

Any participant who has difficulty understanding the information in the consent will be asked to review the misunderstood portion(s) and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Research staff members will work closely with study candidates in an effort to help them understand the requirements of their participation. Persons with literacy problems will be assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the consent is excluded from study participation.

7.3 Screening/Baseline

After signing the informed consent, the participant will proceed through the screening/baseline phase. The screening/baseline phase, which includes assessments on study day 1, prior to randomization, will last a minimum of three days. Based on the targeted 12-19 day inpatient/residential stay following randomization, 14-day programs need to randomize on day 3 while 28-day programs need to randomize on day 10. In order to accommodate staffing patterns for weekends and holidays, the following two exceptions may be made for this study:

1) 14-day programs - Study participants whose Day 3 occurs on a weekend or holiday may be randomized on Day 4 (but no later)
2) 28-day programs - Study participants whose Day 10 occurs on a weekend or holiday may be randomized either on the previous business day or the next business day, whichever is nearer to Day 10.

Participants who meet study eligibility criteria and complete screening/baseline will be randomly assigned to the buspirone or placebo condition.

7.4 Active Treatment Phase

The active treatment phase is 15 weeks. During this time, participants in both treatment conditions will participate in the substance-abuse treatment typically offered by the CTP. Participants will receive buspirone or matching placebo during study weeks 1 through 15. Participants in both conditions will meet with study staff twice weekly to complete study assessments as outlined in Table 3, with the constraint that visits occur on nonconsecutive days.

Table 3: Overview of Study Assessments and Procedures

Assessment/ Procedure	Time Est (Min)	Scrn/ Base	Active Treatment Phase															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Buspirone/Placebo	5		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contingency Management	5		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Screening Assessments																		
Informed Consent	25	X*																
Demographics	5	X*																
CIDI-SAM	20	X*																
Blood chemistry	2	X*																
Birth Control Assessment	2	X*																
Medical History	15	X*																
Substance Abuse Tx Status	5	X*																
Drop-out Risk Assessment	5	X*																
PRISM -Suicide and Homicide	5	X*																
Safety Assessments																		
Adverse Events	5	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HADS	2	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy Test	2		X*			X				X				X			X	
Prior/Concom Meds	5	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Suicidal Ideation Assess	1	X^{+}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	5	X^{+}	X	X	X		X		X		X		X		X		X	
Weight	1	X*								X							X	
Efficacy Assessments																		
Urine for UDS	2	X^{+}	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	
Timeline Follow-Back and cocaine binge assessment	5-12	X*	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
ASI-Lite	45		X*															
ASI-Lite Follow-up	30																X	
WHOQOL-BREF	5	X*															X	
Risk Assessment Battery	15	X*															X	

Assessment/ Procedure	Time Est (Min)	Scrn/ Base	Active Treatment Phase															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Process Assessments																		
Drug Stroop	15	X*		X														
OCDUS	5	X*		X						X							X	
CCQ-Brief	2	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adherence Assessments																		
Med Adhere-MEMS-CM	5		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Med Adhere-Self-report	2		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Med Adhere-Pill count	3		X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	2X	X
Urine for 1-PP measure	1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Assessments																		
Locator Information	5-10	X*								X								
Drug Short Index of Problems	2	X*								X							X	
CRAC Questionnaire	5	X*								X							X	
Fagerström	2	X*															X	
FrSBe	10	X*															X	
Thoughts about Abstinence	4	X*															X	
Assessment Time Est. (min) ♣		200	100	78	58	55	58	53	58	73	58	53	58	55	58	53	139	17
Administrative Forms																		
Eligibility- Randomization	20	X*																
Missed Visit Form•	5																	
Treatment Tracking Form	10		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Termination	5																	X

Notes: Retrospective screening/baseline measures will assess the period before inpatient/residential admission; "X*" = once during screening/baseline; "X^{+}"=at each screening/baseline visit; "X" represents a procedure or assessment performed once per Week; "2X" represents a procedure or assessment performed twice per Week. The research visits for study weeks 1 and 2 will be scheduled to occur while the participant is still in inpatient/residential treatment; ♣The estimates provided for the active treatment weeks reflect the total amount of time for the week (i.e., for the two visits combined). •A Missed Visit Form is completed for each visit that is completely missed by the participant.

7.5 Week 16 Visit

A single visit will be scheduled in week 16 in order to obtain the participant's substance use status and medication adherence throughout the entire study week 15. The measures to be collected during this visit are delineated in Table 3.

7.6 Medication and Trial Discontinuation

7.6.1 Medication Discontinuation

An investigator may discontinue a participant's medication if he or she deems it clinically appropriate or, at the discretion of the investigator, for any of the reasons listed below.

1. Significant side effects that are likely to have been caused by the study medication
2. Serious or unexpected AEs which would make further study medication dosing not in the participant's best interest
3. Inability or unwillingness of the participant to comply with the study protocol
4. Serious intercurrent illness
5. Pregnancy

A participant may discontinue medication anytime s/he wishes. Although the participant may withdraw entirely from the study, s/he will be strongly encouraged to continue attending visits at which safety and other outcome measures are assessed. Participation is entirely voluntary and participants may drop out or have their medication stopped at any time. Any participant who discontinues the study prematurely, regardless of the reason, will be requested to return for a final visit during week 15 to perform the necessary procedures listed in Table 3 and obtain data for end of study/early termination. Whenever a participant stops coming to the clinic without notification, staff will make a concerted effort to contact the participant (or the designated contact person if the participant cannot be contacted) to assure that they have had no untoward effects from study participation and encourage them to return for their scheduled assessments unless they have requested that they not be contacted. In an effort to maximize attendance at visits including follow-up, public database searches and social media (text messaging, e-mail, Facebook, Twitter, MySpace, Google +, etc.) may be utilized. Each social media source will be utilized in the most confidential manner possible based upon the set-up and functionality of the method. The consent form will inform participants about the potential use of social media as a contact mechanism and they will have the option of opting out of its use.

Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Participants will be asked to sign a general consent for the release of information to the referred health care provider. Study staff may request transportation for emergency treatment of a participant if medically appropriate (e.g., for acutely psychotic or suicidal participants).

7.6.2 Trial Discontinuation

The study sponsor has the right to discontinue the investigation at any time.

7.7 Maintaining and Breaking Study Blind

The decision to break the study blind for an individual participant should be made by the medical monitor after consultation with the Lead Investigator if possible, but should be considered only in cases of pregnancy or life-threatening emergency when knowledge of the treatment group investigational agent will influence clinical management.

7.8 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of retail scrip or vouchers. It is recommended that participants receive a total of $75 for completing screening/baseline. During the active treatment phase, there are two visits per week, one of which is fairly short, comprised of collecting urine for the UDS and completing the TLFB and cocaine binge assessments. The other weekly visit will be longer and include the assessments in Table 3. The recommended reimbursement schedule for these visits is outlined in Table 4. Since the week 15 long visit will be substantially longer than any of the other visits, it is recommended that participants be reimbursed a total of $55 for that visit, as outlined in Table 4. Using the recommended schedule, a participant could be reimbursed a maximum of $1,030. However, participant reimbursement might vary across study sites to take into account local IRB guidelines, as well as special circumstances and geographic differences across sites. The Lead Node should be informed of any changes in level of participant reimbursement.

Table 4: Reimbursement schedule for research visits

Visit	Total per Visit ($)	Total # of Visits	Grand Totals ($)
Screening/baseline			75
Longer visits wks 1-14	35	14	490
Shorter visits wks 1-15	25	15	375
Longer visit week 15	55	1	55
Week 16 visit	35	1	35
Total			$ 1,030

8.0 STUDY MEDICATION

8.1 Buspirone

Buspirone hydrochloride, manufactured by Bristol-Myers Squibb Company, will be used. It is available in 5, 10, 15, and 30 mg tablets. It is a white, crystalline, and soluble in water; its chemical formula is $C_{21}H_{31}N_5O_2$•HCl and its molecular weight is 422.0.

8.2 Placebo

Placebo tablets will be identical in color and size to the buspirone tablets.

8.3 Dispensing Study Medication

Medications will be dispensed weekly. Participants will be provided extra medication that may be needed due to holidays or missed visits.

8.4 Storage

Study medication will be stored in compliance with state law and institutional policy.

8.5 Record of Administration

Drug-accountability records including perpetual inventory, will be maintained at all times. These will include a record of the number of buspirone/placebo tablets transferred between areas of the study site (from pharmacy to clinic and back, for example), and those dispensed to and returned by an individual participant.

8.6 Used/Unused Supplies

Unused study medication will be returned to the pharmacy (or other appropriately qualified entity based on local/state regulations) and logged into a perpetual inventory of study drug returned. The study staff will accurately maintain study drug accountability records.

8.7 Side Effects of Buspirone

The most commonly observed AEs associated with buspirone (i.e., at a rate ≥ 5%) that were not seen at an equivalent rate among placebo-treated participants are dizziness, nausea, headache, and nervousness. The AEs most commonly resulting in medication discontinuation (approximately 10% of 2200 subjects in premarketing studies) include central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, and feeling lightheaded; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients who discontinued medication had more than one complaint, none of which could be characterized as primary. Rare allergic reactions have been reported.

8.8 Concomitant Medications

Any medication (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study ideally should be approved by the medical clinician. Grapefruit and grapefruit juice inhibit the metabolism of buspirone and, thus, can dramatically increase blood levels of buspirone; participants should not alter their baseline grapefruit or grapefruit juice consumption without first consulting with the study medical clinician. The following medications should be used only after careful consideration by the medical clinician.

1. In vitro findings suggest that buspirone is metabolized by cytochrome P450 3A4 (CYP3A4) and should be used cautiously with inhibitors or inducers of CYP3A4. When used with a potent inhibitor of CYP3A4, a low dose of buspirone is recommended while a higher dose is recommended if used in combination with a potent inducer of CYP3A4. CYP3A4 inhibitors include: protease inhibitors (ritonavir, indinavir, nelfinavir), antibiotics (erythromycin, telithromycin, clarithromycin, chloramphenicol), azole antifungals (fluconazole, ketoconazole, itraconazole), nefazodone (antidepressant), bergamottin (constituent of grapefruit juice), aprepitant (antiemetic), verapamil and diltiazem (calcium channel blockers). CYP3A4 inducers include: phenytoin (anticonvulsant), mood stabilizers (carbamazepine, oxcarbazepine), barbiturates (phenobarbital), non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, etravirine), rifampin (bactericidal), modafinil (stimulant), hyperforin (constituent of St Johns Wort), cyproterone (antiandrogen, progestin).

2. Potential drug interactions between buspirone and psychotropic agents have been evaluated for several agents and interactions were found with diazepam, haloperidol, and trazodone. The manufacturer notes that potential drug interactions between buspirone and many other psychotropic medications have not been evaluated and thus combining buspirone with other CNS-drugs should be done with caution. Psychotropic medications are exclusionary for this study (see section 6.4.2.2) and ideally should not be started during the active study phase.

8.9 Treatment Plan

8.9.1 Buspirone/Placebo

Study participants will be randomly assigned to receive either buspirone or matching placebo. The dose escalation schedule for this study, conducted under observation, is given in Table 5. The target at study day 10 is to achieve the highest tolerated dose not exceeding 60 mg. Participants who are unable to reach the 60 mg dose or who need to be reduced from 60 mg due to tolerability will be maintained on 15 mg, 30 mg, or 45 mg, whichever is the highest dose tolerated. Participants who are discharged from inpatient/residential treatment prior to study day 10 will be assessed for tolerability by a medical clinician prior to dose escalation and will follow a similar schedule for escalation to that followed in the inpatient/residential treatment setting. Participants will be instructed on how to take the investigational agent and will be instructed to bring their MEMS bottles to every study visit.

Table 5: Buspirone/Placebo Dose Escalation

Study Day	Dose (mg)
1 -3	10 mg (5 am, 5 pm)*
4 - 6	20 mg (10 am, 10 pm)
7 - 9	40 mg (20 am, 20 pm)
10	60 mg (30 am, 30 pm)

**The am dose on study day 1 may occur as late as 2:30 pm, with the second dose at least 8 hours later*

8.9.2 Contingency Management for Medication Adherence

Past research suggests that complete adherence to a prescribed medication regimen frequently fails to occur in clinical trials and that cocaine-dependence trials are no exception (Mooney et al., 2004). A lack of adherence in medication clinical trials is, of course, troubling in that it negatively impacts the internal validity of the study. In the present trial, assuring good medication adherence likely will be made more challenging by buspirone's required twice daily dosing. A randomized controlled trial by Sorensen et al. (2007) found that contingency management, in which vouchers were given for medication adherence, significantly increased medication adherence in HIV-positive, methadone-maintained individuals. More specifically, the MEMS, which utilizes a microchip in a medication bottle cap to record the times and dates of bottle openings was used to assess adherence, with adherence defined as a bottle opening occurring within four hours of a prescribed medication dose (i.e., two hours before or after the dose was to be taken; Sorensen et al., 2007). The present trial cannot reinforce participants for taking their medication since it is potentially coercive to pay participants to take a medication that may not benefit them. However, patients report that a primary reason for failed medication adherence is that they simply forget to take doses (Stone, 2001; Osterberg and Blaschke, 2005); thus, reinforcing bottle openings should help remove a common barrier to medication adherence.

The present trial will utilize a procedure similar to that of Sorensen et al. (2007) but with the addition of a bonus for consecutive instances of adherence, which has been used in other CM protocols (Schmitz et al., 2010). The target behavior for the present protocol is adherence defined as a bottle opening occurring within six hours of a prescribed medication dose (i.e., three hours before or after the dose was to be taken). Consistent with Sorensen et al. (2007), the CM plan for the present trial will involve a relatively quick escalation of the reinforcement value as a strategy to promote consistent opening of the medication bottle. In the present study, participants will receive $0.50 for partial adherence (i.e., one bottle opening within a scheduled time-frame, except for study day 1 in which they will receive $0.25 for partial adherence), with reinforcement values escalating based on full adherence (i.e., two bottle openings within the scheduled time-frames). Specifically, participants will receive $0.50 for study day 1 full dose adherence, with consecutive full adherence resulting in increasing values leading to a reinforcement value of $5 per day on study day 12, which will be maintained through the end of the active treatment phase as long as full adherence continues. A $20 bonus will be awarded each time the participant is fully adherent on each of the seven days of a given study week. Throughout the 15-week active treatment phase, the reinforcement amount will be reset to $0.50

if the MEMS reveals that the bottle was not opened according to schedule. Following such a reset, the escalation of the reinforcement value would follow the original schedule (i.e., as if the participant was at study day 1). A perfectly adherent participant would earn a total of $798.50. Past studies of CM for medication adherence have provided reinforcers in the form of gift cards or other goods (Sorensen et. al., 2007; Carroll et. al., 2002; Carroll et. al., 2001; Preston et. al., 1999), cash (Seal et. al., 2003; Rigsby et. al., 2000), or both (Schmitz et. al., 2010). Reinforcements in the present study will be provided in the form of retail gift cards (minimum $5 value), with the provision of cash for reinforcements under five dollars.

8.9.3 Treatment as usual (TAU)

All participants will receive psychosocial treatment as usually provided by the inpatient/residential and outpatient programs in which they are enrolled (i.e., TAU). For the inpatient/residential phase, the minimum allowable TAU is at least one therapeutic activity daily (including milieu therapy) for 12 - 19 days. For the participants' post-discharge treatment, the minimum allowable TAU is defined as at least one hour of individual or group therapeutic activity per week through study week 15.

In order to characterize TAU at each site, the study team will interview one or more staff at each site using the Addiction Treatment Inventory (ATI; Carise et al., 2000). The ATI is a comprehensive survey designed to characterize addictions treatment service delivery units (SDUs). SDUs refer to a single treatment modality (e.g., inpatient, outpatient, etc.) at a single site. The ATI will be completed either in person or by phone, which is consistent with the administration guidelines for the instrument (Carise et al., 2000). As noted in section 6.5.2 (*5. Substance-abuse Treatment Attendance*), participants' attendance of TAU, defined as the ratio of the number of treatment hours attended to the hours scheduled, will be assessed based on clinic records of treatment attendance.

9.0 ANALYTICAL PLAN

9.1 Overview

The present protocol includes a two-stage evaluation of buspirone, relative to placebo, as a cocaine relapse-prevention treatment. In the first stage, a pilot study will be completed to obtain information needed to design the full-scale trial (e.g., information about medication tolerability, adherence, missing data rates, etc.). As noted in section 6.2, data analysis for the pilot study will be completed in two phases, with the first phase focusing on the data needed for planning the full-scale trial (e.g., information about feasibility, primary outcome, medication tolerability and adherence, TAU characteristics at each site, etc.). This staged approach to data analysis will serve to minimize the time between the end of data collection for the pilot study and initiation of the full-scale trial. The results from the pilot study will be used to modify the design, procedures, medication dosing, and analytic plan of the full-trial as needed.

9.2 Statistical Hypotheses

9.2.1 Primary Hypothesis

The primary hypothesis is that the buspirone, relative to placebo, participants will have a significantly longer period of continuous cocaine abstinence (see section 6.5.1).

9.2.2 Secondary Hypotheses

It is also hypothesized that:

1. buspirone, relative to placebo, participants will have better drug-abuse outcomes during the active treatment phase including:
    - a significantly longer time to first cocaine use (see section 6.5.2).
    - a significantly greater percentage of participants with cocaine-free weeks (see section 6.5.2);
    - a significantly greater percentage of participants with drug-free weeks (see section 6.5.2);
    - significantly fewer cocaine-use and substance-use (i.e., alcohol and/or illicit drug use) days as assessed by the TLFB;
    - significantly less cocaine binging as assessed by the amount of cocaine used and the length of time spent using;
    - better compliance with substance-abuse treatment defined by a greater proportion of scheduled hours attended;
    - significantly greater decrease in ASI-Lite composite scores between baseline and end of treatment;
    - significantly greater decrease between baseline and end of treatment in sexual risky behavior as assessed by the sex risk scale of the RAB;
    - significantly greater increase in quality of life as measured by the physical health, psychological, social relationship, and environment domains of the WHOQOL-BREF
2. buspirone, relative to placebo, will positively impact the process measures as indicated by:
    - a significant decrease in the cocaine interference score of the drug Stroop
    - a significant decrease in the OCDUS total score
    - a significant decrease in the CCQ-Brief total score

9.3 Intent-to-Treat and Evaluable Participant Populations

The intent-to-treat population is defined as the participants who are randomized to treatment. The evaluable population is defined as eligible participants who are randomized, complete at least two-weeks of inpatient/ residential treatment, and have a medication adherence rate of at least 75% for study weeks 1-15. Adherence for each study week will be defined as the most conservative estimate yielded from the three measures of medication adherence that are obtained for both buspirone and placebo participants (i.e., MEMS, pill count, and self-report).

9.4 Analysis Plan

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) and evaluable populations. Major differences in the results for the ITT and evaluable populations, if any, will be further explored. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data. Constraints such as non-linearity, non-normality, etc. may lead to different

but more appropriate approaches to analysis. All statistical tests will be conducted at the 5% Type I error rate (two-sided). When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the multiple testing issues and will interpret results with caution.
Below we provide an analysis plan specifically to address the goals of the pilot Study (Section 9.4.1). Details provided in the remainder of section 9.4 apply to analysis of variables for both the pilot study and the full-scale trial.

9.4.1 Pilot Study

The present protocol includes a two-stage evaluation of buspirone, relative to placebo, as a cocaine relapse-prevention treatment. The pilot study will be completed to obtain information needed for tolerability-related outcomes, which include the following:

1. Proportion of participants reaching maximum dose.
2. Proportion of participants reaching target dose in 10 days.
3. Proportion of participants with a permanent dose reduction.
4. Proportion of participants discontinued from medication.
5. Proportion of participants with a sustained dose at maximum.
6. Sustained dose for those not at maximum (mean and SD)

Each of these will be obtained and a confidence interval calculated using the binomial proportion for items 1-5 and using the normal distribution for item 6.

Medication adherence will also be evaluated in the pilot study including the following:

1. Proportion of medication taken – Self report evaluated using binomial proportion.
2. Proportion of medication taken – Pill count evaluated using binomial proportion.
3. Proportion of medication taken – MEMS evaluated using binomial proportion.
4. Proportion of Urines Positive for 1 – PP evaluated using binomial proportion.
5. Association between 1 – PP and other measures of adherence will be evaluated using Cohen's kappa measure.

The data from the pilot study will also be used to check the assumptions regarding the distribution (mean, SD, shape) of the primary outcome measure, drop-out rates, and various other parameters involved in the sample size calculation/analyses and/or other design elements of the full-scale trial (e.g., reasons for ineligibility, randomization rate, TAU characteristics at each site, etc.). The results from the pilot study will be reported to NIDA and the DSMB. The pilot study data will be used to modify the design, procedures, medication dosing, primary outcome, and analytic plan of the full-scale trial as needed.

9.4.2 Primary Outcome

The primary hypothesis is that buspirone, relative to placebo, participants will have a significantly longer period of continuous cocaine abstinence as assessed by TLFB and UDS. Both assumptions and algorithms are required for defining cocaine use (abstinence). First, for cases where there is a missing UDS, assumptions are required for the timing of the missing UDS in order to define the intervals, as there is an expectation of 2 UDS samples per week. Second, an algorithm to combine TLFB and UDS so as to classify each day as positive, negative, or missing for cocaine use, is required. Finally, an algorithm to account for

handling missing data is required. The approaches to handling these three issues are described in detail in the protocol's SAP. Continuous cocaine abstinence will be measured from the beginning of week 4 (day 22) through day 7 of study week 15. We expect the maximum days of continuous cocaine abstinence to roughly follow a gamma distribution. Data will be analyzed using generalized estimating equations (GEE) assuming a gamma distribution, identity link function and fixed site effect. The following statistical model will be used for the analysis.

$$E(Y_{ij}) = \beta_0 + \beta_1 * CUF + \beta_2 * Treatment_i + \beta_3 * Site_j + \beta_4 * LOS$$

where, Y_{ij} is the maximum days of continuous cocaine abstinence for the k^{th} participant (subscript k suppressed for clarity in the model statement above) in the j^{th} site on the i^{th} treatment, and CUF is the baseline cocaine use frequency (<10 days or ≥ 10 days of use in the 28 days prior to inpatient/residential admission) and LOS is the length of stay prior to randomization (continuous variable 2-9 days). The statistical significance of β_2 will determine the primary outcome of the trial.

To account for missing data (assumed Missing at Random or MAR), once the final data are available, the analysis will be repeated 5 times based on the method described in the protocol's SAP. The final results (parameter estimates and covariance matrix) will be obtained from the 5 analyses by using SAS Proc MIANALYZE. The following is the summary of the workflow:

- Use the algorithm for combining TLFB and UDS so as to classify each day as positive, negative, or missing.
- Obtain values for each missing day's observation for Δ=0 (MAR assumption), as described in the SAP calculate the maximum days of continuous cocaine abstinence and repeat 5 times to obtain 5 complete data sets.
- Analyze each of the five data sets using the GEE model with gamma distribution.
- Generate statistical inferences about the parameters of interest by combining the results from the 5 models using the SAS MIANALYZE procedure.

Note that the primary analysis for the parameter of interest (maximum days of continuous cocaine abstinence during the 12 week outpatient treatment phase weeks 4-15) inference is based on the MAR assumption. A secondary analysis of the primary outcome measure (maximum days of continuous cocaine abstinence during the 12 week outpatient treatment phase weeks 4-15) will also be presented as a function of Δ (the sensitivity parameter for MAR vs Missing not at Random (MNAR) assumption, see Protocol's SAP) which will allow us to assess robustness of conclusions to the deviation from the MAR missing data assumption.

9.4.3 Secondary Outcome Measure

Several secondary analyses that will further elucidate the efficacy of buspirone, relative to placebo, as a cocaine relapse-prevention treatment have been included in this study. For the secondary outcome measures: (1) time to first cocaine use a Cox proportional hazard model will be used, for (2) Cocaine-free/ Drug-free weeks a generalized estimating equation procedure will be used and for (3-11) a mixed effects model will be used to analyze the data incorporating appropriate covariates. Missing data will be addressed as outlined in the previous section and described in the Protocol's SAP. The main goal of all the secondary analyses is to assess the efficacy of buspirone for various secondary outcome measures. Each model for secondary outcome response variables 3-11 will be adjusted for possible site differences by including site as a random effect. The SAS procedure MIXED will be used for continuous variables. Before modeling is commenced, assumptions of linearity will be examined.

1. Time to First Cocaine Use

Time to first cocaine use is defined as the number of days between inpatient/residential discharge and the date on which the first cocaine use occurred. The manner in which TLFB and UDS will be combined to determine first cocaine use is delineated in section 9.4.2.

A Cox proportional hazard model will be used to assess whether buspirone reduces the hazard of cocaine use relative to placebo, while accounting for the variability associated with site and the baseline stratification variable of Cocaine use frequency. Assumptions of the model will be checked via both graphical approach (Kaplan-Meier survival curves and complementary log-log plot) and goodness of fit tests. We will fit time to relapse using the Cox proportional hazard model with Treatment, Site and Treatment-by-Site interactions as the explanatory variables and baseline cocaine use frequency as the stratifying variable. Considerations for including the length of stay prior to randomization and the treatment-by-site interactions in the final model are described in the protocol's SAP.

2. Cocaine-free/Drug-free Weeks

Cocaine-free/Drug-free Weeks during study weeks 4-15 will be considered as a discrete (use or no-use per week) outcome measure. A longitudinal analysis (for weeks 4-15) using generalized estimating equations will be conducted to compare the cocaine-free and drug-free weeks reported during the active treatment phase as a function of treatment group.

3. Cocaine-use and Substance-use Days

Cocaine-use/Substance-use Days during study weeks 4-15 (e.g., potential range of 0-84) will be considered as a continuous outcome measure. A mixed effects model analysis will be conducted to compare the cocaine-use and substance-use days reported during the active treatment phase as a function of treatment group.

4. Cocaine Binging

A mixed effects model analysis will be conducted to compare separately two outcomes, the amount of cocaine used and the length of time spent using during the active treatment phase, as a function of treatment group.

5. Ratio of Treatment Hours Attended to Hours Scheduled

The ratio of the number substance-abuse treatment hours attended to the number of hours scheduled during the active treatment phase will be analyzed using a mixed effects model analysis with the log of the number of scheduled hours and the type of treatment (inpatient/residential, intensive outpatient or outpatient) as covariates.

6. The ASI-Lite

The seven areas of functioning measured by the ASI-Lite (medical status, employment status, drug use, alcohol use, family status, legal status, psychiatric status) will be analyzed using a mixed effects model with treatment as a covariate. These seven tests will be performed without adjustment for multiple testing.

7. Sexual Risky Behavior as Assessed by the RAB

The sex risk scale of the RAB, which produces a score ranging from 0-28, will be considered as a continuous response variable, and treatment effect will be analyzed using mixed effects model.

8. Quality of Life as Assessed by the WHOQOL-BREF

The WHOQOL-BREF provides a score (0-100) for four domains: physical health, psychological, social relationship, and environment. The four domains will be analyzed using a mixed effects model with treatment. Significance of treatment is declared if the treatment (as defined by a change in log-likelihood) is significant ($p<0.05$). These four tests will be performed without adjustment for multiple testing.

9. Attentional Bias as Assessed by the Cocaine Interference Score of the Drug Stroop

The cocaine interference score of the drug Stroop, which ranges from -5999 ms to 5999 ms, will be considered as a continuous response variable and treatment effect will be analyzed using a mixed effects model.

10. Drug Compulsivity as Assessed by the OCDUS Total Score

The OCDUS total score, which ranges from 0-52, will be considered as a continuous response variable and treatment effect will be analyzed using a mixed effects model.

11. Cocaine craving as Assessed by the CCQ-Brief Total Score

The CCQ-Brief total score, which ranges from 1 - 7, will be considered as a continuous response variable and treatment effect will be analyzed using a mixed effects model.

9.4.4 Process Measures Analyses

In addition to evaluating buspirone's impact on the process measures (see section 9.4.3), we will evaluate the process measures as potential mediators of treatment effect using methods proposed by Baron and Kenny (1986) and Judd and Kenny (1981) and the statistical test proposed by Sobel (1982).

9.4.5 Safety Analyses

1. Adverse Events

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group. The incidence of adverse events and serious adverse events by type will be compared between treatment arms using either Fisher's Exact test or Chi-Square analysis as appropriate; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available.

2. Vital Signs

Repeated measures mixed models will be used to compare the treatment groups on blood pressure and heart rate from screening/baseline through study week 15.

3. The Hospital Anxiety and Depression Scale (HADS)

Repeated measures mixed models will be used to compare the treatment groups on depression and anxiety symptoms, as measured by the HADS, from screening/baseline through study week 15.

9.4.6 Missing Data

For the primary outcome measure, missing data will be addressed as described in the protocol's SAP. These same methods for handling missing data will be applied to secondary outcomes related to abstinence.

9.5 Sample Size Estimate

9.5.1 Pilot Study

As noted above, the first stage of the present project entails the completion of a pilot study in order to obtain information needed to design the full-scale trial (e.g., information about medication tolerability, adherence, missing data rates, TAU characteristics at each site, etc.). In selecting the sample size for the pilot study we sought to include the minimal sample required to provide reasonable estimates on which to base the full-scale trial. Specifically, based on an analysis of two key areas for which information will be obtained, medication tolerability and primary outcome, a sample size of 60 (30 per arm) would provide moderately precise estimates for the full-scale trial. The medication tolerability assessments largely involve the proportions of participants meeting a given criterion (e.g., the proportion reaching maximum dose, etc, see Section 9.4.1). For all possible proportions (i.e., 0.0 – 1.0), the margin of error is below 0.2. For the primary outcome measure, Table 6 provides the margin of error as a function of standard deviation and differences between the mean maximum days of continuous cocaine abstinence in the two arms (see Section 9.5.2 for details on the selection of the difference in mean maximum days).

Table 6: Margin of Error for Primary Treatment Effect as a Function of Treatment Group Difference and Standard Deviation

	Mean and SD of Buspirone Arm and Difference in Days*		
	Mean=20, SD=15 Diff*=6 days	Mean=18, SD=10 Diff*=4 days	Mean=16, SD=5 Diff*=2 days
95% Confidence Interval Margin of Error	4.13 days	2.76 days	1.37 days

Note: * Difference in days is equal to the difference between the mean maximum days of continuous cocaine abstinence in the buspirone and placebo arms.

9.5.2 Full Scale Study

As noted above, a pilot study will be completed to provide information needed to more accurately calculate the sample size for the full-scale trial. The present section provides an initial estimate of the sample size required for the full-scale trial based on several assumptions. Assuming a gamma distribution for the maximum days of continuous cocaine abstinence (as described in Section 9.4.2), we simulated data and analyzed them using generalized estimating equations (GEE) with a gamma distribution and identity link function. Considerations for sample size and power were based on detecting a difference between the two arms corresponding to Cohen's d of 0.4 and 0.3 (see Table 7). For all the simulations we chose 14 as the mean maximum days of continuous cocaine abstinence for the placebo arm based on the findings from a cocaine relapse-prevention trial completed by Jones et al. (2004). The standard deviations were assumed to be the same in both the arms.

Table 7: Power to detect a treatment effect size of .4 or .3 as a function of sample size, difference between treatment arms, and standard deviation

Mean and SD of Buspirone Arm for Cohen's d of .4			
Sample Size	Mean=20, SD =15 Diff* = 6 days	Mean=18, SD=10 Diff = 4 days	Mean=16, SD =5 Diff = 2 days
150	76.8% (19%)	70.6%	69.1%
200	86.2% (12%)	81.2%	80.8%
250	92.1% (7%)	88.8%	88.6%
Mean and SD of Buspirone Arm for Cohen's d of .3			
Sample Size	Mean=18.5, SD =15 Diff* = 4.5 days	Mean=17, SD=10 Diff = 3 days	Mean=15.5, SD =5 Diff = 1.5 days
250	73.8%	68.1%	67.1%
300	80.5%	74.9%	74.4%
350	85.6%	80.5%	80.3%

Note: * Difference in days is equal to the difference between the mean maximum days of continuous cocaine abstinence in the buspirone and placebo arms.

The power calculations in Table 7 are based on 10000 simulations using the GEE model including the covariates - Treatment, Site, Cocaine use frequency (CUF) and Length of Stay (LOS) as described in the primary outcome section 9.4.2. Parenthesized figures indicate percent of cases that failed to converge, when convergence failure rates exceeded 5%. Power is calculated excluding non-convergent cases. Based on these power calculations, the optimal sample size is estimated to be 250 (125 per arm), as this sample size is consistent with detecting a moderate difference between the two arms, corresponding to Cohen's d = .4, with 80% power over varying assumptions on the standard deviation of distribution of the primary outcome. Powering the study to detect a Cohen's d of 0.3 may result in detecting a treatment difference that may be not clinically meaningful. We expect a loss-to-follow-up rate of 5% from those study participants who do not provide any primary outcome data after release from the residential program, and the estimated sample size based on this assumption results in the need to increase the sample for the full-scale trial to 264 participants to account for the attrition. The pilot study will provide important information about the variability of the primary outcome, which is a major determinant of sample size, and the loss-to-follow-up rate and thus, might result in a change in the sample size estimate for the full-scale trial.

9.6 Descriptive Statistics

Summaries of the characteristics of the participant population in both treatment arms at screening/baseline will be prepared for the intent-to-treat and evaluable participants. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups.

9.7 Interim Analyses

In coordination with the centralized Data and Statistics center (DSC), formal interim analyses for efficacy and futility are planned as described below for the full scale trial. The timing of the formal interim analyses depends both on the recruitment patterns and the timing of primary outcome data collection. Although the recruitment pattern is unpredictable, we are expecting 1.6 participants randomized per site per month on average, with 6 sites enrolling. Enrollment of the 264 participants is expected to be completed over approximately 27 months. Information concerning the primary outcome measures will accrue as participants

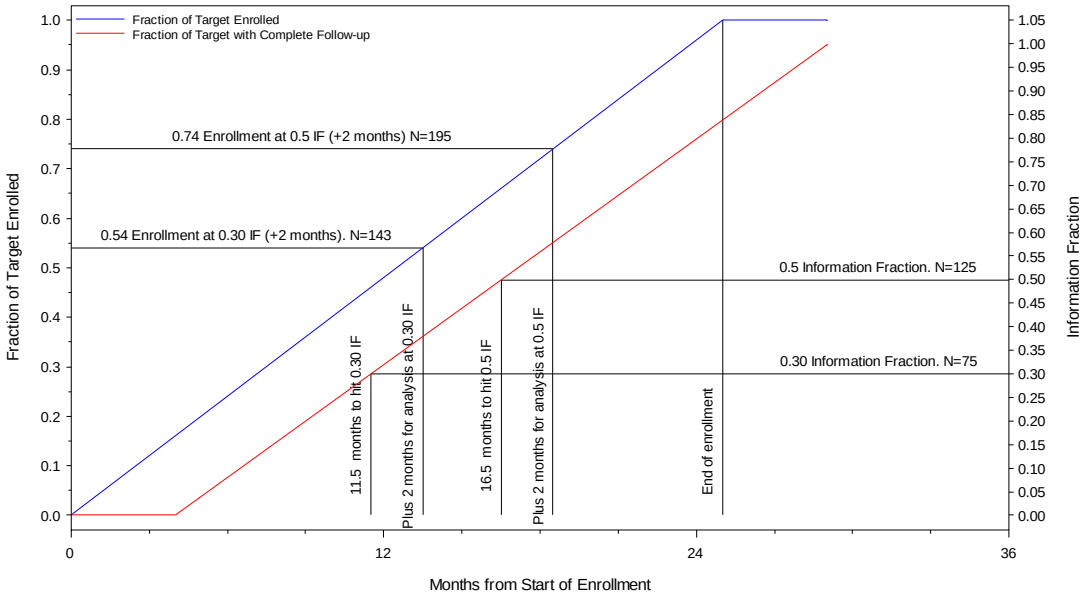
complete the 16-week visit and thus the "information fraction" is the percent of the final sample size contributing to the primary outcome analysis.

Interim analyses for efficacy and futility will be performed and reported to NIDA and the DSMB. Interim testing will be carried out using the Lan-DeMets interim monitoring boundary with an O'Brien-Fleming-type spending function, in which only small amounts of alpha are spent prior to the final analysis. The DSMB and NIDA will also consider early stopping for lack of benefit or for futility, with an approach based on conditional power to estimate the likelihood of statistical significance given the observed efficacy results and various possible choices for the remaining results. Futility analyses will coincide with interim analyses for efficacy.

Because of the information expected to be gained from the pilot study, with one of its goals to provide estimates of the error variance and mean of the primary outcome of maximum days of continuous cocaine abstinence, there are no plans to perform sample size re-estimation during the trial.

Figure 5 below depicts the timing of the interim monitoring analyses assuming enrollment of 264 participants over approximately 27 months, measuring outcome at 16 weeks, and a loss-to-follow-up rate of 5% from those participants who do not provide primary outcome data after release from the residential treatment program. The timing of the interim analyses will be set prior to the end of enrollment such that if a conclusion is reached based on efficacy or futility to stop the trial early, a good proportion of the study population will not need to be enrolled. We also assume a 2-month period to perform the analyses and for decisions to be made by the DSMB and NIDA. From this, we plan two times for interim analysis when the fractions of final sample size providing primary outcome data endpoint are at 30% and 50%, corresponding to 11.5 and 16.5 months after enrollment started, respectively. According to the O'Brien Fleming boundaries, an alpha of 0.00009 and 0.00297 will be spent at 30% and 50% information fraction, respectively, leaving an alpha of 0.04695 for the final analysis. With this large size of alpha left for the final analysis, the estimate of the sample size does not need to be increased for interim monitoring. Further, at these interim analyses time points, and accounting for the 2-month deliberation period, approximately 54% and 74% of the study population will have been enrolled. If recruitment takes longer than expected, modifications can be made to the timing of efficacy and futility analyses based on guidance from the DSMB and NIDA.

Figure 5. Information Fraction and Fraction of Target Enrollment for Proposed Interim Analyses Based on Months from Start of Enrollment



9.8 Minority/Gender Analyses

In accordance with NIH guidelines, repeated measures mixed model and GLMM analyses will be completed to determine whether treatment response was significantly affected by participant minority/gender status using an interaction term for treatment, time and minority/gender as appropriate.

9.9 Reliability and Validity of Assessments of Cocaine related adverse consequences

Analyses to evaluate the reliability and validity of the SIP-D and the CRAC will be completed.

9.10 Post-hoc Analyses

In addition to the analyses described above, a number of post-hoc analyses will be completed.

10.0 REPORTING AND MONITORING

Statement of Compliance
This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

Regulatory Files
The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for the regulatory documents compliance prior to study initiation, throughout the study, as well as at the study closure.

10.1 Informed consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the lead node (LN) prior to the site initiation visit. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

Prior to signing the informed consent form, research staff who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read. If the participant is interested in participating in the study, a researcher who is authorized to obtain informed consent by the PI and if applicable by the IRB, will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. The participant will consent by signing and

dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. The consent must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Persons delegated by the PI to obtain informed consent must be listed on the Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

In order to ensure that potential study participants understand the research study, a comprehension "quiz" (referred to as a comprehension tool) may be administered to potential participants prior to the informed consent being signed. If the potential participant misses an item on the quiz, the research staff will re-review that information to ensure understanding of study procedures and may have the person re-take the consent quiz prior to signing the informed consent document. The content of the quiz may be modified per local IRB requirements.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty.

Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

Investigator Assurances

Each community treatment program site (CTP) must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

10.2 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol must comply with their Institution's policy regarding conflict of interest.

10.3 Clinical monitoring

Investigators will host periodic visits by NIDA contract monitors who will ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant.
Qualified node personnel (Node Protocol Managers and/or QA monitors) will provide site management for each site during the trial. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

10.4 Study documentation

Study documentation includes all data-related forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

10.5 Safety Monitoring

10.5.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

10.5.2 Protocol Violations Reporting and Management

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The protocol's Lead Investigator in conjunction with the CCC will make the decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation. The consequences will be specified and participating sites should be informed.

All protocol violations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Violations CRF. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

10.5.3 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary. Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

10.5.4 Adverse Events (AEs)

At each site, the study physician will review each Serious Adverse Event (SAE). These reviews will include an assessment of the severity and causality to the study drug or study procedures. The study physician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The medical monitor will determine which safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. This will include all suspected adverse reactions that are serious and unexpected. The study staff will be trained to monitor for and report adverse events and Serious Adverse Events.

Each of the CTPs has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

10.5.4.1 Definitions of Adverse Event and Serious Adverse Event

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and relationship to therapy and processing are described in Appendix A.

10.5.4.2 Reportable Serious Adverse Events

For the present study, the following SAEs will not be recorded in the data system; these events will be reported to local IRBs according to local IRB guidelines.

- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery
- Admission to inpatient/residential substance abuse treatment

11.0 DATA MANAGEMENT AND PROCEDURES

11.1 Design and Development

This protocol will utilize a centralized Data and Statistics center (DSC). The DSC will be responsible for the development of the case report forms (CRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Ideally, a web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

11.1.1 Site Responsibilities

The DSC will specify the data management responsibilities of each individual CTP.

11.1.2 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities, 2) provide final CRFs for the collection of all data required by the study, 3) provide data dictionaries for each CRF that will comprehensively define each data element, 4) conduct ongoing data validation and cleaning activities on study data from all participating CTPs through database lock.

11.2 Data Acquisition and Entry

Completed forms and electronic data will be entered into the data management system in accordance with the CRF Completion Guidelines established by the DSC. Only authorized individuals shall have access to electronic CRFs.

11.3 Data Editing

Data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated and distributed to treatment programs for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system. Data status reports ideally will be issued monthly to assist the site, the corresponding RRTC (node) and the lead investigator to monitor the site’s progress in responding to queries.

11.4 Data Transfer/Lock

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

11.5 Data Training

The training plan for CTP staff includes provisions for training on assessments, CRF completion guidelines, and computerized systems.

11.6 Data QA

To address the issue of data quality, the DSC will follow a standard data monitoring plan. An acceptable data quality level prior to any database lock will be given as part of the data management plan. Data quality summaries will be made available during the course of the study.

12.0 PUBLICATIONS AND OTHER RIGHTS

Protocol development and implementation in the NIDA CTN is a collaborative process. The publication plan for the current protocol will comply with the CTN Publications Subcommittee's guidance on publications. Individuals making substantive contributions to the protocol development and implementation will have opportunities to participate in publications. Other contributors will also be acknowledged.

13.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____

INVESTIGATOR (S)

• I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of participants.
• I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
• I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
• I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
• I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.
• I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

Typed Name	Signature	Date
_____	_____	_____
Principal Investigator		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		
_____	_____	_____
Sub-Investigator		

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15.0 APPENDIX A

15.1 Definition of Adverse Event and Serious Adverse Event

Adverse Event: An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. (Any change from baseline in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator are considered AEs.)

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

Serious Adverse Event (SAE): A serious adverse event (SAE) refers to all serious events including serious adverse events or serious suspected adverse reaction or serious adverse reaction as determined by the study investigator or the sponsor is any event that results in any of the following outcomes:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of the study, whether or not considered treatment-related, must be reported.

2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.)

3. Inpatient hospitalization or prolongation of existing hospitalization

4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5. Congenital abnormality or birth defect

6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Unexpected Adverse Event: Any adverse event, the specificity or severity of which is not consistent with the investigator brochure or the package insert. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy: All pregnancies that occur on study will be captured on a pregnancy CRF and not separately reported as an AE or a serious event. Women who become pregnant during the study period will be discontinued from further study drug/intervention referred for medical care, and the pregnancy followed until an outcome is known. Women who terminate the pregnancy may be reinitiated on study medication based on study physician judgment. Women who become pregnant will be eligible to continue study assessments.

Medical History: A thorough medical history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site's Role in Eliciting and Reporting Adverse Events: Appropriately qualified and trained research personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical

and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Research personnel will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting serious events to their IRB, per their IRB's guidelines.

Sites are required to enter reportable AEs and SAEs in to the study's data capture system. Additional information may need to be gathered to evaluate the SAE and to complete the appropriate CRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stabilized at the time of initial reporting or if new information becomes available, follow-up information must be submitted as soon as possible.

Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study.

15.2 Assessment of Severity and Causality

A designated study medical clinician will review reportable AEs and SAEs for seriousness, severity, and causality on at least a weekly basis.

Guideline for Assessing Severity: The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guideline for Determining Causality:

The study investigator will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

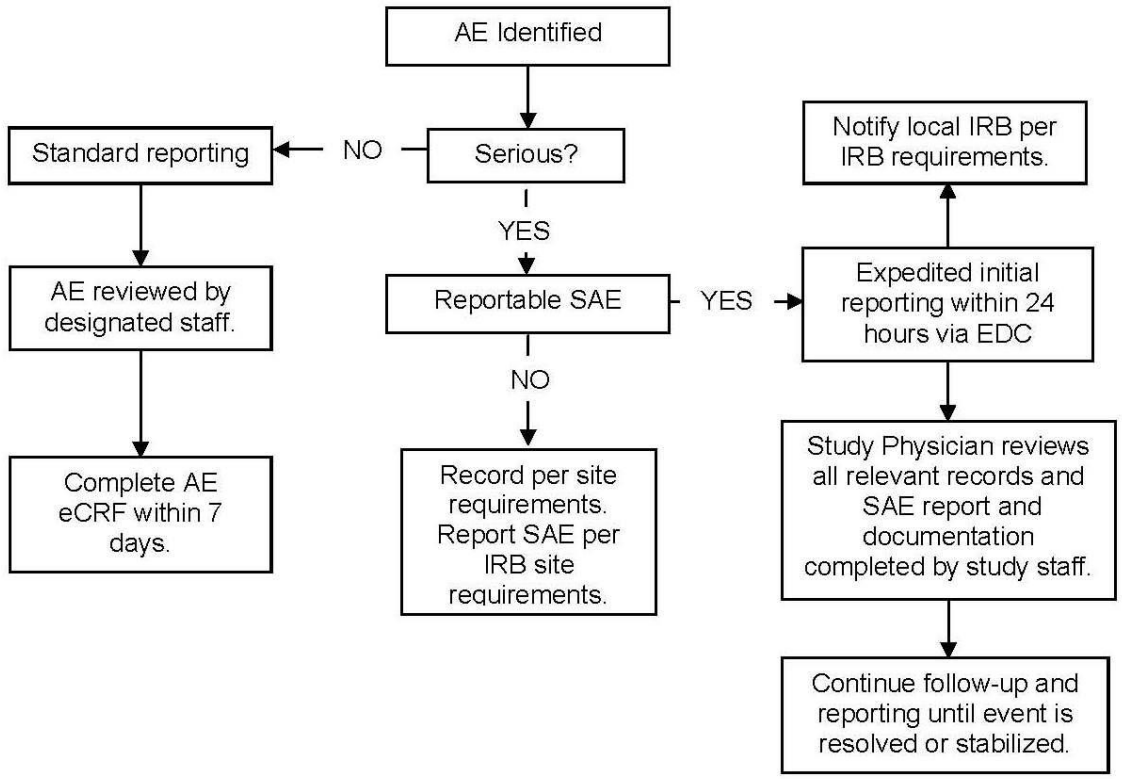
15.3 Reporting and Management Procedures of AE/SAEs

Site AE/SAE Monitoring: Protocol monitors as well as local node staff will review the study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately by the research staff. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Sponsor's role in Safety Management Procedures of AEs/SAEs: A NIDA-assigned Medical Monitor is responsible for reviewing all SAE reports. All reported SAEs will generate an e-mail notification to the Medical Monitor. All SAEs will be reviewed by the Medical Monitor in the study's data capture system and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the medical monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, FDA and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor, DSMB and FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Reporting to the Data and Safety Monitoring Board: The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Participant Withdrawal: The site investigator in consensus with a study physician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be discontinued from study drug/intervention. The site investigator should consult with the lead investigator and/or Medical Monitor as needed. If necessary, a site investigator may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to complete an end of study visit assessment and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or their condition becomes stable.


AE Identified
Serious?
NO
Standard reporting
AE reviewed by designated staff.
Complete AE eCRF within 7 days.
YES
Reportable SAE
YES
Notify local IRB per IRB requirements.
Expedited initial reporting within 24 hours via EDC
Study Physician reviews all relevant records and SAE report and documentation completed by study staff.
Continue follow-up and reporting until event is resolved or stabilized.
NO
Record per site requirements. Report SAE per IRB site requirements.